Volume XIX Number 2

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

FEBRUARY

1958

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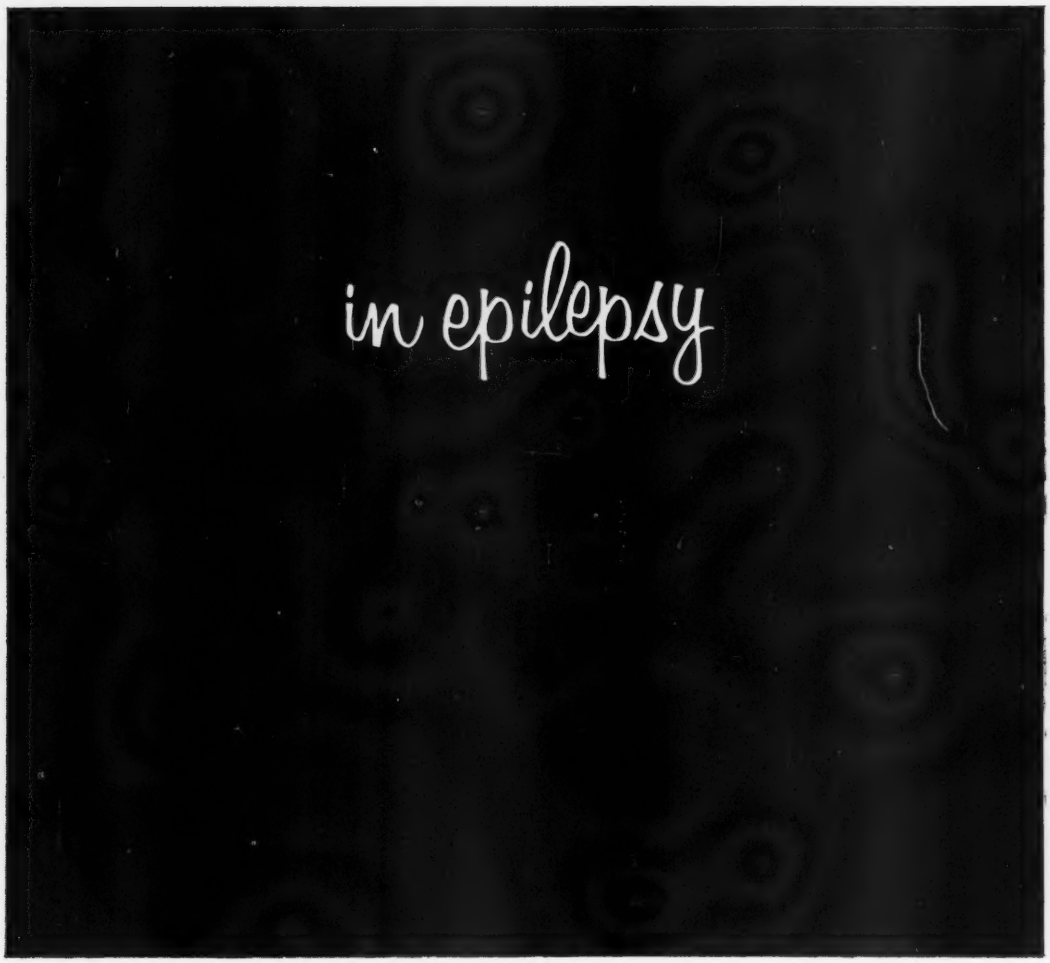

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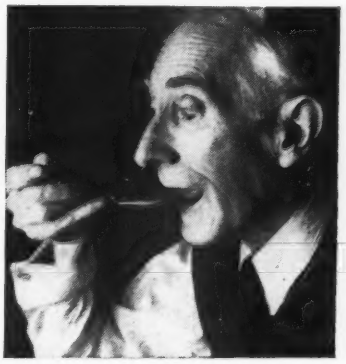

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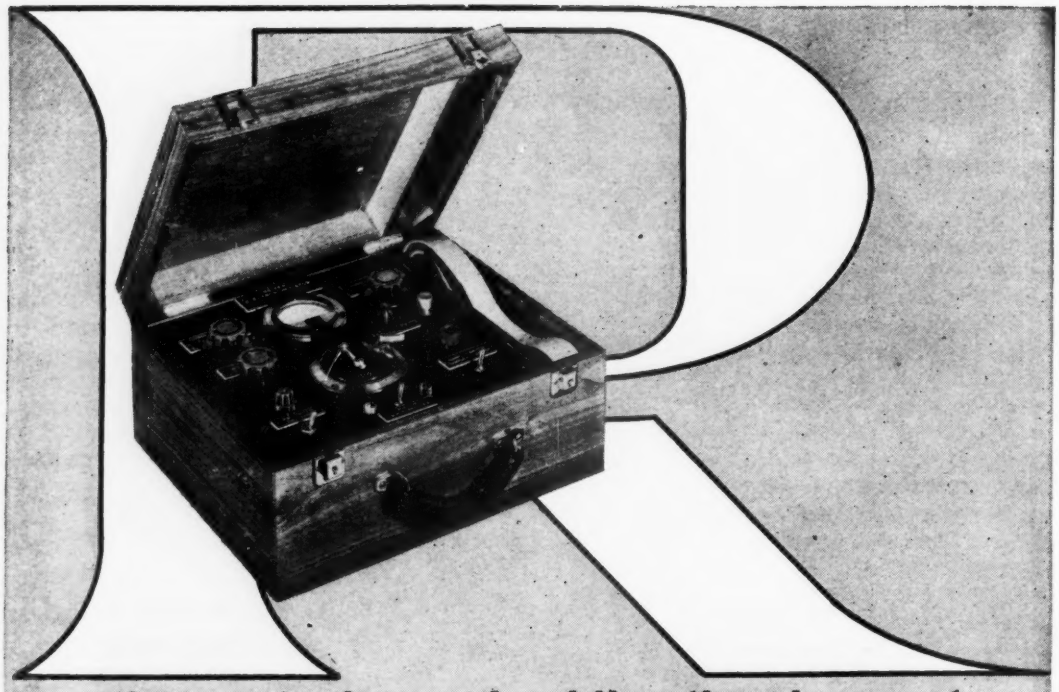

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1. Sainz, A.: Personal communication.
2. Hutchinson, J. T.: Evaluation of Pacatal in Psychotic States, address before the American Psychiatric Association, Nov. 16, 1956.
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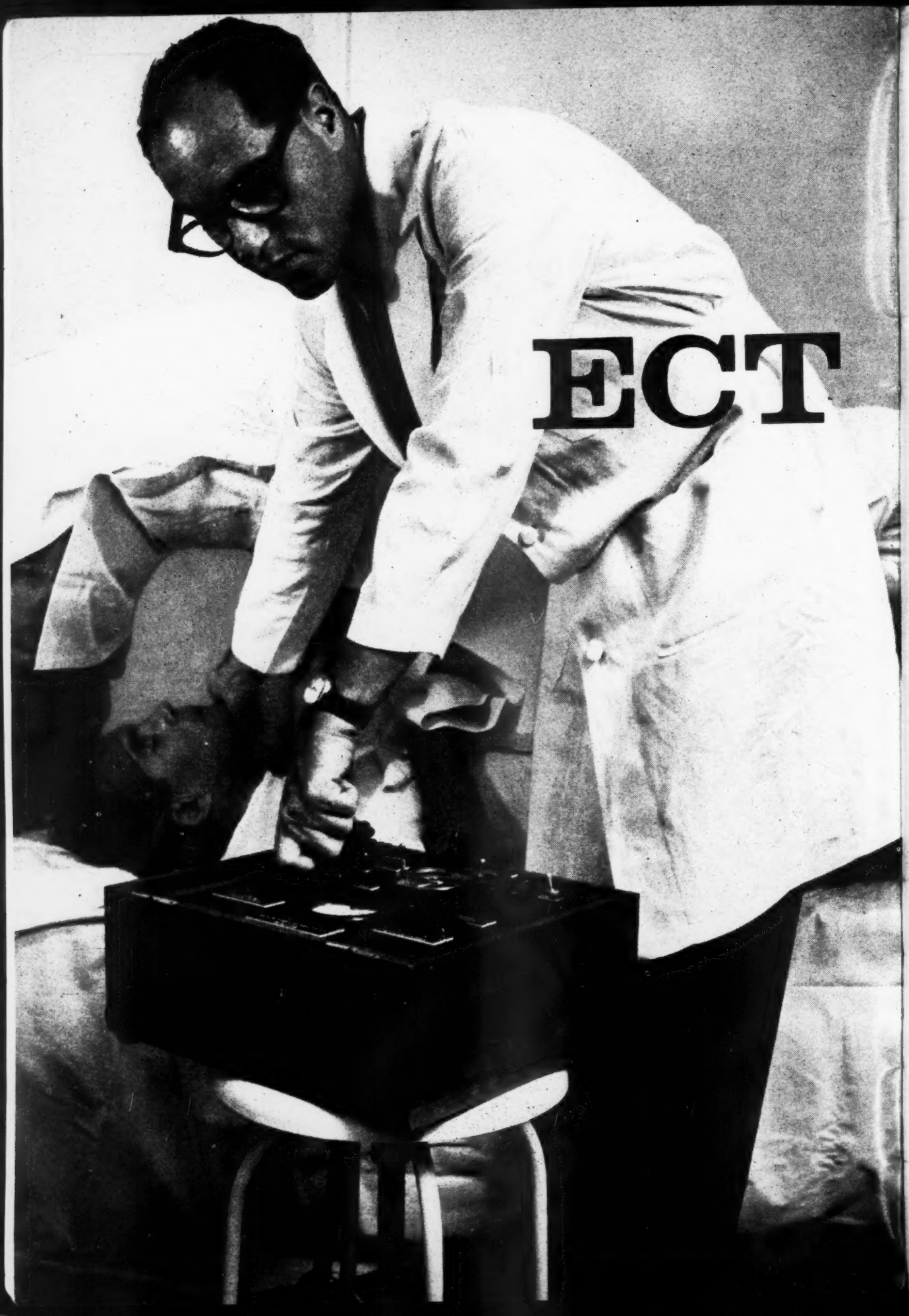
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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Effect of Rauwolfia Alkaloids and Related Substances on Chromatophores. I.

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WILLIAM J. TURNER, M.D.

In an earlier paper[1] it was reported that the melanophores of fish dilate following immersion of the living animal in solutions of dispersion of the granules in chromatophores which gives the appearance of dilatation of the cell. Shortly thereafter it was found that 11-desmethoxyreserpine (raunormine, deserpidine, recanescine) and rescinnamine share this property with reserpine. At this moment we learned that Brodie, Shore and Pletscher[2] had evidence that these three Rauwolfia alkaloids were also alike both in their capacity to release serotonin from the central nervous system and in possession of tranquilizing action. Their data agreed with ours also in that other sedatives and tranquilizers did not exhibit the same set of three properties. At this point then it might have seemed justified to suggest that the effect on the melanophores was medicated through serotonin release. However, it had been known since the time of Osterhage[3] that yohimbine, a very close relative of reserpine, causes nuptial coloration following injection into fish, and we were able to show that it dilated the melanophores of fish following immersion; but Brodie, Shore and Pletscher had, in one animal, not found tranquilizing effect nor serotonin release. Further, Abramson and Evans, in their first paper on the effects of LSD on *Betta splendens*[4] and later Cerletti and Berde[5] working with the female guppy, *Poecilia reticulatus,* had observed melanophore dilatation of fish immersed in LSD. The latter authors added to the list BOL (the monobrom derivative of LSD), the laevo-isomer of LSD, and methergine (methyl-ergobasine). Of these only BOL is reported to have any sedative effect.[6]

Another difficulty in assuming that the action of reserpine, raunormine and rescinnamine was due solely and always to serotonin release was already suggested by the assertion of Erspamer[7] that among Teleosts and Elasmobranchs enterochromaffin cells, as well as serotonin, are lacking. Then, Correale[8] later showed that in three species of fish the acetone-soluble substance from brain which constricted the clam heart was, in two instances, not inhibited by dibenamine, and in the third, partly inhibited; therefore it was presumably not serotonin. As to this we must be cautious, until further study will clear up the matter. However, early in 1956 Carlsson and Hillarp[9] demonstrated that intravenous reserpine caused complete liberation of the catechol amines from the adrenal medulla of the rabbit. Erspamer wrote in a private communication that others had found changes in the neurosecretory cells of the hypothalamus. Later in the year Holzbauer and Vogt reported depression by reserpine of the noradrenaline concentration in the hypothalamus of the cat,[10] and Waalkes and Weissbach[11] demonstrated in vivo release of histamine from rabbit blood by the same compound. Clearly, the mode of action as well as the possible sites of action of reserpine and its congeners may be various. The present communication concerns some further aspects of this variation.

Action of Neurohumors on Melanophores

Parker,[12] in his very thorough review of the literature named many agents the injec-

From Research Division, Central Islip State Hospital, Central Islip, N. Y.

tion of which results in dilatation of melanophores of invertebrates, of fish and of amphibia. It should be noted that fish tend to assume a color approaching that of their background; for instance, bottom dwellers turn light or dark depending upon the color of the substrate, and this is done in large part by modification of the degree to which the melanophores are expanded or dispersed. The expansions appear to be due in part to release from constricting influences exerted by adrenergic impulses, arising from excitation by light of the upper half of the retinae, mediated by the central nervous system; in part, however, by cholinergic impulses of local excitation, and in part by the action of the melanophore stimulating hormone (intermedin) of the hypophysis. The adrenal gland plays a part in the melanophore activity, probably due not only to its catechol amines, but it may be suspected also, due to steroids which modify salt or ionic balances. All of these are under complex control by the nervous system, the pineal gland, sex hormones and possibly other modifiers. Constriction follows excitement of fish. It follows therefore that many cholinergic compounds will tend to expand the melanophores, adrenergic compounds to constrict them; drugs with only secondary effects on the nervous system may have variable actions.

With the discovery of serotonin, and the evidence that it may be an ancient neurohumor[13] of a somewhat adrenergic nature, the possibility opened up, which Parker could not have known, that a third order of neurohumors could play a role in animal color changes. Indeed, in our hands, serotonin led to constriction of melanophores *in vivo* and *in vitro:* 0.006 mg. of serotonin in Spaeth's solution (6 vol. 0.1N NaCl, 1 vol. 0.1N KCl and 0.35 vol. 0.1N $CaCl_2$ had neither constricting nor dilating action on the melanophores[14]) injected just beneath the scales produced a local constriction lasting half an hour. When a tail fin was cut off, its melanophores dilated. A serotonin solution, 0.001 mg./ml., led to contraction beginning in 10 minutes. Injection of 0.0001-0.001 mcmg. reserpine beneath scales led to local dilatation lasting up to 36 hours.

Action of Reserpine on the Melanophores of Fish Immersed in Drug Solutions

Reserpine is active by mouth, as are raunormine and rescinnamine. Serotonin is not; nor is serotonin capable of producing any change of melanophores, or of behavior, in fish immersed in solutions up to about 500 mg. per liter. To determine whether other agents, potentially active orally, might be found to have melanophore-dilating action following immersion, a large number of natural and synthetic substances have been tested. These were dissolved in water or in alcohol, then dispersed in water. The concentrations rarely went above 100 mg. per liter, since our concern was chiefly with demonstration of effects in the order of magnitude of the reserpine dosage. The water was purified by passage through a demineralizer, then permitted to stand for a week or more, usually with several fish in it to insure its suitability. Usually the volume of water contained in a gallon jar was 1 liter. A number of species of fish were employed in efforts to find those most sensitive to the action of reserpine. As was stated in our first paper, *Aequidens portalegrensis* would show the effect with 0.4 mcgm. per liter on 6 hours' immersion, but the young of *Cichlasoma biocellatum* and of *Cichalasoma meeki,* or of *Tilapia macrocephala,* were equally sensitive. All tests were run at pH 6.6-7.0, at temperatures between 72° and 84° F. In every instance the fish were illuminated from above, with a white substrate. Evaluation was done on fish after 30-60 seconds of excitation.

In Table 1 is a list of the drugs which were found to have a dilating action on melanophores following immersion of the fish in solution for six hours or less. An asterisk marks those compounds reported by Cerletti and Berde, which we have not examined, but whose data have been recalculated to conform to ours; except that their data was based on two hour immersion. We feel that they fit well with our observations.

Many pure compounds were tested and found lacking in melanophore activity under the conditions of the test. Among the indole compounds, which were tested at concentrations of 20 mg./l. or higher, were: serotonin (500 mg./l.), ethyl- and 1-ben-

zyl-2, 5-dimethylserotonin, harmine, reserpic acid, methyl reserpate, ajmaline, serpentine, isoreserpine, gelsemine, rauwolseine, strychnine and ibogaine. Attempts to bring out a melanophore dilatation by addition of isoniazid or Marsilid or W-1544, as amine oxidase inhibitors, were unsuccessful, although N,N-dimethyltryptamine had a weak potentiating action on reserpine. We have tested so far some 20 phenothiazine compounds, among which are chlorpromazine, Promazine, Adazine, Perphenazine, Phenergan and Pyrrolazote; none altered the melanophores up to lethal concentrations except that some dilatation took place concomitant with preagonal activity. No action was shown by mescaline, nor by 3, 4, 5-trimethoxybenzoic acid. Antihistamines, of which we tested more than a dozen, including Pyribenzamine and Chlortrimeton were also ineffective. Adrenaline, nor-adrenaline, Isuprel and their corresponding red oxidation products (produced by adding the free bases to the water in which the fish swam, so that the particles would be taken up in the mouth and then ejected, with consequent rapid oxidation) had neither dilating nor constricting effects on fish melanophores. Frenquel was not effective, nor was Ritalin, nor any of a large number of sedatives (e.g., chloral hydrate, phenobarbital, seconal, amytal, bromides or Sedormid). Regarding Sedormid, it may be added that chronic intoxication did not lead to appearance of porphobilinogen or porphyrins in the water. We tested a considerable number of anticonvulsants, including Dilantin, Mesantoin, Thiantoin and Tridione, to the limits of solubility, without effect. Convulsants, such as picrotoxin, Metrazol and camphor, were ineffective. Agents which block adrenergic activity, such as Regitine, Apresoline and Priscoline, were ineffective, as were those which block cholinergic activity, such as atropine, hyoscine and arecoline. Agents with cholinergic activity were likewise without action, such as pilocarpine, physostigmine, mecholyl. Veratrine, veratramine and a mixture (Protobore, Penick) of protoveratrives A and B were ineffective. Three preparations of cannabinols, pure at the time of preparation, were supplied; they were insoluble in water; we added one to fish food, the others were added to the water in alcoholic solution to form a fine colloidal dispersion. There was no effect on melanophores, nor on behavior. Bufotenine had a weak contracting action on melanophores, as did N. N-dimethyltryptamine and the related 2-methyl, 3-(2 diethylamino ethyl) indole and 3-(3 dimethylamino propyl) indole. Injections of these agents caused intense blanching, and they were active contractors of melanophores *in vitro*.

We were supplied with crude extracts of many plants from different parts of the world; some of these had never been tested for biological activity, although they were known to contain alkaloids. Regarding only those of whose nature we had some idea, or which were of well-identified source (authentic specimens collected by trained botanists) we believe we are justified in submitting our report.

No action took place on melanophores on immersion in solutions or dispersions prepared from extracts, of the following:

Acidenthera
Aconite
Adhatoda vasica
Adonis vernalis
Agaric, white
Agrimony
Alder, black
Alder, red
Alkanet root
Alstonia spectabilis
Artocarpus altilis
Aspidosperma oblongum
Aspidosperma quebrachblanco
Bacopa monnieri
Banaba
Banisteriopsis caapi
Caesalpinia crista
Calotropis procera
Cassica reticulata
Celastrus paniculatum
Clerodondron indica
Clerodendron serratifolium
Damiana
Dicenta spectabilis
Embelia ribes
Ervatamia punctata (2 fractions)
Eupatorium villosum
Forsteronia floribunda
Heliotropum florum
Hyptis capitata
Kava kava
Morina citrofolia
Moringa pterygosperma
Nordostackys jatamansi
Parthenium hysterophorus
Pathomorphe peltata
Peganum harmala
Petiveria alliacea
Peyote buttons
Piptadenia peregrina (cohoba) oil
Rejova aurantia, tertiary bases
Rhabdadenia biflora
Salaci reticulata
Sankhpuspi
Smilax balbisiana
Solanum torvum
Strophanus kombe
Tabernaemontana
Thevetia meriifolia
Tourefortia hirsutissima
Withania somnifera
Yam, wild

The following plant extracts led to dilatation of melanophores, similar to that caused by reserpine:

Bekkaweri (possibly the Singhalese name for *Rauwolfia serpentina*).

Aspidosperma quebracho (this is known to contain yohimbine).

Ochrosia elliptica (limit of response with crude preparation ca. 200 mcgm./1.)

The following plant extracts led to dilatation of melanophores, but with limitation to deep, or to superficial, or other local variations: *Althea;* Masterwort; *Saussurea lappa; Rivea cuneata;* one fraction of *Alstonia spectabilis,* tertiary bases; *Ochrosia elliptica,* queternary bases; one fraction of the bases of *Ervatamia punctata.* These observations have not yet been followed up.

The following extracts led to contraction of the melanophores, which could be demonstrated by maintaining the fish over a black substrate: *Aletris; Centelela; Lantana camara; Muira puama; Ormosia jamaicensis; connessi* bark; *Urechites.* Defatted *Cohoba* from *Piptadenia peregrina* caused contraction, which was overcome by 150 mcgm. per liter of rescinnamine.

From the experimental evidence so far, we can say with some assurance that the only compounds capable of inducing melanophore dilatation in the concentrations of the order of 1 mgm. per liter or less under the conditions of the test are the alkaloids of the reserpine group or of the LSD-BOL group. Regarding *Ochrosia elliptica,* we have no further knowledge of structure.

Is Reserpine Action Limited to Melanophores of Fish?

Among invertebrates and vertebrates there are a number of different kinds of cells which are subsumed under the designation chromatophores.[12] Even among one family of teleosts there are great variations in the number and nature of these, and in their individual responses to even a single influence, such as light. Parker discussed lipophores, allophores and guanophores. The lipophores which contain yellowish pigments, such as xanthophyll, have been called xanthophores; those containing reddish pigment, such as astaxanthin, have been called erythrophores.[15] Allophores appear to differ from lipophores only in the insolubility in alcohol of their pigments. While both lipophores and allophores have been described as having the same ability to dilate and to contract as do melanophores, there is evidently much variation in the factors which induce these changes; they often respond in ways the reverse of the melanophores. At times there is a strong suggestion that dilatation occurs under the influence of sex hormones, or in conjunction with sexual activity; certainly nuptial coloration and aetivity are coeval. In the Elritz of Germany[16] and in the red-bellied dace *(Chromosomus eos)*[17] erythrophores dilate under the influence of the melanophore stimulating hormone, intermedin. Guanophores which contain little guanine have been called leucophores; in these the granules are motile. In those guanophores where the guanine exists in large, birefringent plates it is non-motile; these cells are iridescent, particularly if furnished with a background by dilatation of melanophores, and have been called iridiocytes or, with their related melanophores, the group has been called iridiosomes. Actually, as Parker has said, an almost endless variety of combinations may occur among the cells.

Among other vertebrates the same kinds of cells may occur, but each family seems to differ slightly from other families in respect to the factors governing the behavior of these color cells. Does reserpine have an action on melanophores of all orders? This can be answered in the negative, in that among several species of frogs, and their larval forms, gathered on Long Island, injection into the lymph sacs of solutions of reserpine and of raunormine, even up to 0.1 mg., had little effect on the color of frogs maintained in the light. These drugs did not enhance the dark-adaptation, nor did they impair the return to the light-adapted state.

Is the action of reserpine on chromatophores limited to melanophores? To this, the answer is a qualified no. It usually happens that red, green and blue shades of such fish as *Betta splendens,*[18] *Trichogaster trichopterus, Macropodus opercularis* and the fancy guppy, *Poecilia* (Lebistes) *reticulatus,* are enhanced; but in other species, e.g., *Xiphophorus helleri, Rasbora heteromorpha, Tanichthys albonubes* and *Cichlasoma biocellatum,* the enhancement of reds, yellows and

iridescence seems to be due to contrast effects or to the provision of a black background for iridiocytes. In *Tilapia macrocephala* a reddish tinge in fins occurs more clearly with adult fish, but the phenomenon is variable, possibly related to secondary sexual or aggressive display. However, in *Tilapia,* the golden opercular color of the male, or the red opercular color of the female, was never induced by reserpine. The former depends upon the dilatation of xanthophores; the latter upon a contraction of cells which leaves exposed the color of the underlying blood vessels; and both are under the influence of sexual hormones.[19] In the same way, the red coloration of Cichlasoma meeki (Firemouth) did not develop under the influence of reserpine. In this instance the red color which gives the common name to the species is probably due to transfer of pigment from the liver to the erythrophores under the influence of intermedin. Unfortunately we have not been able to secure specimens of red dace or of Elritz, in which this property has been studied.

From the evidence above, reserpine and its equivalents act to dilate or to expand pigment cells, but they do not bring about a transfer of pigment from the liver to the pigment cells. This effect is limited to fish, and in fish the effect on pigment cells other than melanophores is modified by species, age and other factors.

To What Is the Effect of Reserpine on Melanophores Due?

When suitable fish are immersed in solutions of reserpine or equivalent, it usually happens with smaller concentrations there is a very gradual darkening, so that in six hours the entire fish is almost black. Now and then, and this is particularly evident with methyl reserpate acetoacetate, the darkening occurs first at the thinnest parts of the fins, gradually affecting the melanophores in thicker parts in a manner suggesting a consequence of diffusion. Only after several hours does this darkening develop as if from the side of the blood stream. These phenomena are variable, under influences which I have not been able to analyze; but it does seem that there are two modes of action, one local, the other through the blood stream.

The local action is of very obscure mechanism. When a piece of the tail fin is cut off the melanophores instantly dilate, just as they do when a caudal band is prepared. It is possible to cause the melanophores to contract *in vitro* by altering the salt balance, or in a dilute solution of serotonin or adrenaline (approximately 0.1 mcgm./ml.), but thereafter placing them in reserpine solutions does not lead to redilatation. A number of variations of this test have been unsuccessful. When caudal bands were prepared the band blanched after a few days; at seven days reserpine caused melanophores in the band to dilate *in vivo* only from the edge inward, i.e., by a diffusion process. When a section of the tail was cut out, and while the regrown tail was still pale (28 days), the melanophores would dilate *in vivo,* but not *in vitro.* Cutting the cord did not interfere with reserpine effect. It appeared therefore that the local action may only occur with innervated cells. Paul Wright of the Department of Zoology, University of Michigan, whose studies on the melanophores of frog skin are well known,[20] wrote that reserpine had no action on the melanophores, in his preparation.

Since melanophores contract under the action of serotonin, adrenaline, nor-epinephrine and similar compounds both *in vivo* (injection) and *in vitro* and Parker and others have presented evidence that there is in life a balance between the contracting influences of adrenaline and the dilating influences of acetylcholine and of intermedin, it might be thought that release from contracting influences led to dilatation of the chromatophores. This seems to be the most plausible explanation, but the failure to dilate *in vitro* after contraction by serotonin, adrenaline, nor-adrenaline or isopropyl nor-adrenaline, argues against this. It could not be due to histamine release either, for much the same reasons; to which might be added that on injection histamine is a weak dilator of melanophores only within a narrow range, some 10-20 mcgm. per gm. of fish; further, the histamine dilatation shows distinct differences from the reserpine effect.

As an alternate to the theory that reserpine acts by releasing the melanophores from the contracting action of serotonin or catechol amines, or the melanophore constrictor of Hogben,[21] there must be considered the possibility that it acts by increasing the amount of circulating intermedin, ACTH, or gonadotropin, directly or through mediation of, say, release of contents of the neurosecretory material in nucleus supraopticus.[22] At the present time there cannot be a clear answer to this, because of the very confusing state of knowledge in this field. For discussion of this the reader is referred to Parker[12] and to Pickford and Atz.[23] For instance, Umrath and Walcher[24] have reported that none of the chromatophores of *Macropodus opercularis* respond to the action of pituitary preparations, yet with the pure intermedin available to us injection of 3 mcgm. led to immediate dilatation of the melanophores and within 15 minutes to increase of intensity of color in the orange bands; and this is precisely the effect of reserpine. On the other hand, the failure to produce the secondary sexual colorations of *Tilapia,* for instance, argues against intermedin release. ACTH, which has about 1% of the melanophore and lipophore action of intermedin,[25] has not been studied by us, nor have any of the possible adrenal or gonadal steroids which might exert action on chromatophores.

In the light of the above, then, it must be said that the mode of action of reserpine on fish melanophores is obscure, though it appears more likely to be by way of a hypothalamic-hypophyseal endocrine action than by way of simple release of serotonin or catechol amines. It must be admitted that the hypothalamic action, if any could be secondary, mediated by serotonin release. Certainly the fact that the agents which are potent in this phenomenon are indole alkaloids suggests that this portion of the molecule is required to attach at some point on a receptor surface, but beyond this is conjecture. It can however be said that those drugs which are active in man in doses of about 100 mcgm. (reserpine, LSD) are active on fish chromatophores at comparable doses (1-50 mcgm./l.), whereas as serotonin releasers relatively enormous doses must be given (at 1 mg. per kilo, i.e., 70,000 mcgm. for a man).

So far we have said nothing about behavior. Since the demonstration of a specific effect on *Betta splendens* by Abramson and Evans[1] a number of papers have appeared dealing with behavioral effects of drugs on fish.[26,27] It now appears probable that most of the pharmaceutical houses which are currently active in the search for new phrenotropic agents are using fish as one of their test objects. The author has reported[1] that reserpine exhibited quieting action on fish at 12 mcgm. per liter. However, since that was written, much has been learned. Behavior of fish was studied in every test indicated in the body of this report. Dr. Abramson and his associates were kind enough to recheck some of our observations. Beyond this, hundreds of other behavioral studies on undrugged fish were conducted. The usual care was taken to use conditioned water, to control pH, and to keep note of and control over temperature. Variations of volume of space available, numbers of fish per gallon, species, age and sex, illumination, and many other factors were introduced from time to time; on these observations we were able to proceed with drug studies, guided by a very large literature on fish behavior and on toxicity of drugs on fish. Nearly three years of work went into this, but just recently we realized that the drug observations could not be reported, and must be done over.

We do not feel that we can comment either on our own past work or on that of others, except to say that it is always possible to reach a concentration of a drug, or to drug a fish for so long a time, that behavioral disturbances will be manifest. Insofar as we have been able to stay at concentrations and times well below those which impair vital processes we have not seen any sedative action of reserpine or of phenothiazines on fish. We distrust deeply reports recently published which describe the actions of phrenotropic agents on fish. In any event we must note that in fish many actions may occur from drugs which are unrelated to any pharmacological effect on the central nervous system, gills, heart, etc. Noble and Curtis have described, for in-

stance, the effect of the increase in coloration of Jewel fish under the influence of yohimbine on other, undrugged fish.[28]

Of what interest is all this to psychiatrists? First, I think, is the evidence that melanophores, whose properties and origins are so like those of astrocytes, exhibit responses to reserpine administration and to serotonin which could suggest a role in central nervous system function.[29,30] Second, that those agents which are most potent in melanophore dilatation are precisely those which are potent ataractics; while it seems that those which are not quite so active on melanophores have a somewhat different psychic action (e.g., LSD and yohimbine); and that in a still third level we find another kind of CNS action (alcohol and paraldehyde). The meaning of this is obscure, but it may indicate differing modes of action. Third, it can induce caution regarding implication of a relationship between a drug action and schizophrenogenesis, when the action of the drug may be so complex and possibly play only a role in a chain of events. Fourth, there is a suggestion that the phenomena described in this paper relate to a field of neuropharmacology which is still very obscure, namely that of the neurosecretory products of the hypothalamus. Could it be that reserpine will be useful in the study of this subject?

TABLE I

Substances Which Lead to Dilatation of Melanophores of Fish Following Immersion in Solution for Six Hours.

Raunormine	0.2–0.4 mcgm./l.
Reserpine	1.0–4.0 mcgm./l.
D-1, bromo-lysergic acid dietyhylamide (BOL)*	40 mcgm./l.
Rescinnamide	50–80 mcgm./l.
Methyl reserpate, acetoacetate	50–80 mcgm./l.
D-lysergic acid diethylamide (LSD)	1 mgm./l.
Yohimbine	1.6 mgm./l.
Ajmaleine	2.4 mgm./l.
3-epi-alpha-yohimbine	5.0 mgm./l.
Benadryl—2-(Benzhydryloxy)-N, N-dimethylethylamine HCl	10.0 mgm./l.
2,5, dimethyl-serotonin	circa 25 mgm./l.
L-lysergic acid diethylamide*	33.0 mgm./l.
Methyl-ergobasine (methergin)	125 mgm./l.
Paraldehyde	250 mgm./l.
Ethyl alcohol	2500 mgm./l.

*Calculated from the data of Cerletti and Berde.[5]

Summary

It is shown that those *Rauwolfia* alkaloids which are hypotensive and sedative to man in small dosage, namely, reserpine, raunormine and rescinnamine, and which have been shown to be releasers of serotonin, catechol amines and histamine in large dosage, are potent dilators of fish chromatophores in extreme dilution. This response of the fish melanophores is highly specific with respect to the drug causing the response, the cells which respond, and the class of vertebrates whose cells react. There is a local action on innervated cells. A general action is suggested, possibly via hypophyseal hormonal release.

Author's Note: We are indebted to the following sources for drugs which have been tested: Lederle Laboratories, Ciba Pharmaceuticals, the Upjohn Company, Penick & Co., Hoffmann-La Roche, Sandoz Pharmaceuticals, and Dr. D. W. Woolley. A number of biologicals secured on field trips in Asia, Africa, South America and New Guinea were made available to us as extracts through the courtesy of Dr. R. F. Raffauf of Smith, Kline and French. Dr. Paul Bell of Lederle Laboratories presented us with pure intermedin.

Most of the species of fish with which we have worked have been purchased from local dealers in tropical fish. We are indebted to Dr. Lester Aronson of the American Museum of Natural History, New York, for *Tilapia*, from which we bred our own fish for experimental work.

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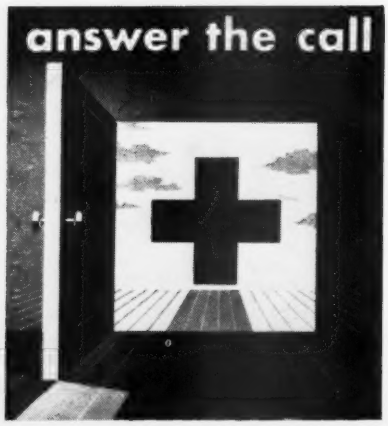

Laryngospasm: Its Incidence and Management in Electro-Convulsive Treatment

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Laryngospasm has been recognized as a possible but rare complication of electroconvulsive therapy. There is little reference to this phenomenon in psychiatric texts or in other books specifically devoted to psychiatric somatic therapies. Workers in the field have recognized the repeated incidence of post shock apnea with the inconvenience that it entails, and have known many patients as "poor breathers," thus complicating further shock therapy.

In most of the clinics general measures to deal with the post shock apnea have been developed, such as alteration in posture, routine suction of posterior pharynx, Reiter electro stimulation, electro stimulation over the phrenic nerve trunks, and wide variety of resuscitation methods with or without oxygen by demand flow. Pre-treatment techniques have likewise been developed, such as administration of pure oxygen before shock, use of muscle relaxants, and the administration of varying doses of atropine by all routes. Bellak[1] refers to respiratory arrest as probably the most frequent complication of electroshock. Sprague and Taylor[2] list respiratory complications as second most frequent complication and caution therapists concerning the necessity of determining adequate airway. Brill and Kalinowsky[3] have stated that respiratory embarrassment is certainly the most frequent disturbance with electroshock and suggest that a variable degree of airway obstruction possibly occurs during the apneic phase. Other writers on the subject of electroshock either fail to refer to laryngeal spasm or in a few instances deny that laryngospasm can be an accompaniment of post shock apnea.

The relationship of prolonged apnea or respiratory failure to recorded deaths is difficult to determine and it is expected that only those fatalities in immediate relationship with the treatment phase would be attributed to electroshock. In a review of several series of fatalities it was determined that the greater number of deaths were recorded by non-specific entities, such as pulmonary collapse, respiratory failure, cerebral anoxia, and status epilepticus. We are in complete agreement with Lewis[4] who felt that the mortality rate with electroshock is probably higher than that reported statistically. He also stated that the fatality was usually ascribed to some other organ than the brain, and in some instances the necropsy failed to reveal the primary cause of death. In the large series of shock cases reported by Kolb and Vogel[5] (75,000 cases) the electroshock complication rate was only 11 per 1,000 treatments and the fatality rate was 0.5 per 1,000 in ECT procedures. Will, et al.,[6] in a study of 33 deaths following ECT reported two attributed to respiratory failure and two other cases with immediate death and the primary cause in doubt. They were of the opinion that it was difficult to adequately evaluate the incidence of death from ECT due to failure in reporting and that frequently the relationship of treatment to death was not clear. In a study by McLay[7] deaths from ECT were reported on a sharp increase in the past several years and suggested that this change could be attributed to an increased boldness in the use of this form of treatment along with a wider use of curare derivatives as adjunctive muscle relaxants. It has been generally agreed that few contraindications to ECT exist and that maintenance ECT can be used in chronic disturbed cases with almost unlimited total number of treatments. If repeated bouts of cerebral anoxia can lead to serious irreparable brain damage, it should follow that some complications or fatalities may very likely be related in a direct or indirect way to such treatments.

For the purposes of this investigation it was determined that the reports of death due directly to ECT in Veterans Administration Hospitals throughout America might give a more accurate statistical appraisal than the further investigation of other vital statistics would bear on the subject. This seemed the more reasonable in view of an existing procedure in the Veterans Adminis-

tration which requires the reporting of all such unusual incidents to Central Office, Washington, D. C. The complete description of the shock procedure, medical course, and pathological examinations, where obtained, were likewise available for careful study. Statistical value of such a study is further enhanced by the fact that the Veterans Administration treats on any one day approximately 55000 psychiatric cases. This would represent about 1/14 of institutionalized cases in this country. It would exclude from predictive estimate the number of ECT's given on an out-patient basis or those treated privately outside of institutions. The Veterans Administration records were studied on 14 reported deaths occurring over a four year period, October, 1950, to October, 1954. Of this number 64% were considered due to respiratory death and in one instance where the laryngoscope was employed a severe spasm of the larynx was the direct cause of death. Six of the fatalities had received muscle relaxants prior to therapy and in only one instance a respiratory death resulted with use of succinylcholine. Three of the respiratory deaths failed to respond to Reiter cerebral stimulation.

One of the fatalities occurred at the Veterans Administration Hospital, Leech Farm Road, Pittsburgh, on August 18, 1954. The patient was a chronic schizophrenic of ten years duration and had received many courses of ECT as well as insulin coma before his admission to Pittsburgh Veterans Administration Hospital. At this institution he required maintenance ECT due to continuous violent behavior. In a period of eight months he had received more than 50 standard ECT's without untoward effects. At 9:00 A.M. after a standard treatment there was prolonged apnea and emergency methods including coramine I.V., adrenalin I.V., and artificial respiration with Pneaphore positive pressure oxygen were unsuccessful in sustaining respirations. After all efforts to establish a better airway were attempted, a direct laryngoscopic examination against great interference from trismus was accomplished , revealing an extreme laryngeal spasm with marked cyanosis. At 10:00 A.M. a tracheotomy was inserted but twenty minutes later all vital signs had ceased. Permission for autopsy was not granted. Reiter cerebral stimulation was given during the first half hour of the above critical period, without effect. This death was considered due to asphyxia resulting from laryngospasm and could possibly have been avoided if a patent airway had been established within the first four minutes of the prolonged apnea.

The next stage in the development of this study was to set up a technique of observing directly the action of the cords and larynx during the complete convulsive phase of ECT. This was accomplished with the aid of consulting anesthesiologists who conducted direct laryngoscopic examinations on two groups of patients numbering twenty in each group. In the first group no pre-medication was given and a lightly induced electroshock was administered for anesthetic purpose. After normal laryngeal function had been reestablished the electroshock was delivered with the scope in place and the entire spasm of the larynx was observed directly. In each instance a laryngospasm of 45 to 60 seconds duration and varying intensity was observed. In the second series of cases atropine I.M. 1/75 to 1/100 gr. was given within 30 minutes of treatment. Satisfactory plane of anesthesia was then obtained with 2½% Pentothal using on an average of 250 to 500 mg. of the barbiturate. After relaxation and approximately 30 seconds before ECT 20 to 40 mg. of succinylcholine were given through the same needle. The patient was bagged easily at this juncture with one or two small volumes of oxygen and the shock delivered. In this group of cases the airway remained patent throughout and the cords showed slight movement initially but moved out slowly in almost a fully abducted position. Breathing did not seem suspended and the patient remained well oxygenated throughout the procedure in marked contrast to those observed in the other group. The laryngospasm observed in the first group of cases was then documented by direct 16 mm. colored movies. These movies were obtained by using a special adapted laryngoscope coupled intermittently to a specifically designed camera.[8] Three cameras were then synchronized to demonstrate the simultaneous status of the

glottis, head and neck, and the exact setting of the shock equipment. These films were then edited and the various stages of laryngospasm were enlarged to 5 inch transparencies which were incorporated along with the above mentioned sequences into an exhibit disclosing the subject of laryngospasm with electro convulsive therapy. This exhibit has been presented at the meeting of the American Psychiatry Society, Atlantic City, New Jersey, May, 1955; before the American Anesthesiology Society, Boston, Massachusetts, November, 1955; and before the American Medical Society, Chicago, Illinois, June, 1956. The endoscopic films obtained for this exhibit will soon appear as part of a Medical Education film sponsored by the Abbott Pharmaceutical Company.

It was concluded from these studies that a laryngospasm of varying intensity and duration occurs during the apneic phase of every electro convulsive treatment in the unpremedicated patient. We believe that prolonged apnea, as discussed by Hull,[9] and later by Jacoby, et al.,[10] may produce fatal cerebral as well as cardiac complications that must be kept in mind as possible sequellae during the post shock period. Modern muscle relaxants that are rapidly hydrolyzed may prevent severe spasm and should be used only by those sufficiently trained in the techniques of resuscitation. Regardless of the methods of premedication and later handling of the apneic patient, the phenomena, if extended beyond the safety period of two to four minutes, will require mechanical methods to immediately assure a patent airway. Such methods are quickly administered within seconds and are life saving during this crucial period when sustaining stimulants and other general methods of resuscitation can be administered in the presence of an assured patent airway. Flagg[11] has recently proved the necessity of controlling apnea and hypoxia to prevent cardiac arrest.

Anatomical and Clinical Significance of Laryngospasm

The larynx from a structural standpoint is the upper expanded portion of the trachea and is made up of a framework of cartilages. These cartilages, joined and flexible, are encased in a series of ligaments and muscles covered by an internal lining of mucosa. These structures are controlled by the sensory and motor components of the vagus branches via the superior and inferior laryngeal nerves. In addition to other functions the larynx is a valvular mechanism that guards the patency of the trachea. This valve has control of the airway and will involuntarily go into spasm if the nerve supply is irritated by either central, peripheral, or local stimulation. This sudden snapping down of the glottis can be immediately serious and may produce fatal cerebral or cardiac complications. Laryngospasm must be differentiated from simple obstruction by the tongue or other bodies, epiglottic impaction, laryngeal edema, or primary vagal hypertonicity. Murtagh and Campbell[12] have shown that experimental laryngospasm may be produced reflexly by stimulation of the laryngeal mucosa, or of any sensory nerve leading from the larynx. Ogura and Lam,[13] stated that stimulation of the laryngeal mucosa would precipitate reflex closure of the cords if the duration of the stimulus and its intensity involved a sufficient number of fibers of the laryngeal nerves. Bates,[14] observed that laryngospasm is a distinct factor in a large percentage of submersion deaths. He points out that hypertonicity of the vagus nerve in hyper excitable individuals is a factor in a large number of laryngeal spasms and that these cases are examples of prolonged laryngospasm out of proportion to the strength of the irritative or stimulating factor. We have concluded in our experience that this explanation may be operative in a great number of prolonged apneas encountered during the procedure of electrotherapy.

The nerve supply of the larynx and its accessory muscles comes from the sensory and motor branches of the 9th and 10th cranial nerves along with the motor branches of the 11th and 12th nerves. Although the vagus supplies the greatest innervation of the intrinsic as well as extrinsic muscles of the larynx, the sensory branches of the 9th joins the branches of the 10th to form the pharyngeal plexus. These four cranial nerves originating in the nuclei of the medulla are associated in their distribution to all parts of larynx as well as to the accessory muscles

of respiration. During the process of ECT there is a discharge of energy through the cortical mantle extending on through the supra nuclear paths to the nuclei of the medulla, and then out over the activating systems mediating the motor end plates of the laryngeal muscles and its associated structures. This sets up powerful contractions of the entire respiratory system including the extra-respiratory elements. In the laryngospasm of electroshock the entire mechanism of breathing is temporarily suspended due to paralysis of the muscles of the larynx and the accessory muscles of respiration. The regulatory mechanism of inspiration and expiration is interrupted thus interfering with the balanced regulation of intake and output as mediated by the vagus receptors of the alveolar ducts described by the Hering-Bruer reflex. In conjunction with the closure of the glottis and spasm of the muscles of respiration there is a slow expulsion of air from the lungs. The contraction of the intrinsic muscles of the larynx, the thyroid and sterno-thyroid cancel out as antagonists and the larynx remains stationary in this phase of incomplete closure. A slight escape of air may take place during this partial closure thus permitting partial artificial respiration in some cases. In a prolonged spasm usually associated with hypertonic vagal mechanism the closure becomes compete and expiration does not take place. It must be borne in mind that curare and its derivatives will enhance a vagal stimulating effect often producing in addition to above the lower bronchiolar constriction that leads to serious asphyxia that requires immediate mechanical aid and direct supply of oxygen. Upon termination of laryngeal spasm the Valsalva phenomenon must be reckoned with and its effects upon a weakened cardiac status may produce cardiac arrest and other serious cardio vascular complications. This phenomenon is the result of intra-thoracic pressure against a closed glottis, impounding increased amounts of venous blood in the extrathoracic vessels. Upon the release of this condition and accompanying asphyxia a large amount of blood enters the heart to place severe stress upon the musculature and impulse conducting system.

Premedication with quick acting barbiturates may be another added factor that promotes laryngospasm and adds to the above physiological considerations. This situation was reported early by Burnstein and Rovenstine,[15] who demonstrated by animal studies that the cords become adducted in spasm or at least show hyperactive adductor tone during barbiturate anesthesia. Recently, Moore and Bridenbaugh[16] have indicated that intravenous Pentothal in lighter planes of anesthesia has always been a serious problem to the anesthesiologist. They report 35 cases with laryngospasm under Pentothal anesthesia. None of the cases responded to positive pressure oxygen and all of the cases responded instantly to intravenous succinylcholine. Baggott,[17] has reported frequently on the high incidence of laryngospasm with rapidly induced anesthesia and makes particular reference to the notorious effect of thiopental. He refers to the "ill met triad" of hypernea, mucus free within the air passages, and hypersensitive trigger zones within the respiratory system as being vulnerable to the effects of rapidly induced anesthesia. Flagg[18] has called attention to the fact that drug anesthetics depress the pharyngeal reflexes and increase the possibility of aspiration leading to glottic spasm and occasional fatality.

Management of Laryngospasm by Mechanical Methods

It must first be conceded that recognition of prolonged laryngeal spasm is the most important step in treatment. Knowledge of the possibilities of aspiration phenomena, tongue obstruction, and a great number of other basic considerations must be reflex in the therapists mind. This along with the rapid execution and smooth performance of resuscitation denotes the capable physician working through any emergency effectively. The following techniques are simple mechanical procedures that require only seconds and provide prompt relief of asphyxia by proper oxygenation and establishment of effective airway.

1. After prolonged apnea and laryngospasm there is a variable reservoir of air in the lungs. The inspiratory phase is blocked and in some instances only a slight release of air is possible upon compression of the thoracic cage. The in-

spiratory phase cannot always be forced by oxygen under pressure yet the simple insertion of two fifteen gauge needles through the cricothyroid ligament will instantly permit escape of air and the delivery of oxygen as needed. This allows an immediate attention to the pharynges, artificial respiration, stimulants, cardiac evaluation and other basic considerations to be completed to definitive ends.

2. Use of a laryngoscope and insertion of an endotracheal tube under direct observation may be difficult due to the severe degree of trismus and associated spasm of the pharyngeal muscles.
3. The use of a Mosher Life Saving tube or other blind indirect methods of intubation may be accomplished with ease after the trismus is overcome by a jaw wedge. These methods may be traumatic to the cords and larynx and require thorough deep suction throughout the process.
4. Injection of 1 cc. of 1% Pontocaine directly through the crico-thyroid ligament is helpful almost immediately by stimulation of a powerful tussic reflex and the relaxing effect of the spray of topical anesthesia.
5. In severe cases of persistent apnea the insertion of the Caparosa Cricothyrotomy Tube[19] can be accomplished in a few seconds. Upon withdrawal of the stylet, an airway equivalent to a #5 tracheotomy tube is firmly in place, permitting immediate resuscitation techniques.

Conclusions

Laryngospasm of varying duration and intensity occurs with every electroconvulsive treatment unless the patient is adequately premedicated.

The etiology of laryngospasm is of many known origins.

Laryngospasm is a challenge and serious complication for the anesthesiologist as well as the electrotherapist.

Succinylcholine chloride effectively combats spastic closure of the glottis.

Electrotherapists should be capable of managing all respiratory complications and should be trained in the use of safer muscle relaxants along with resuscitation techniques.

Approved mechanical methods of management of laryngospasm may require only seconds to administer and should be on the emergency table for proper use.

Many complications considered of primary cardiac or cerebral origin are probably sequellae of laryngospasm.

Quick acting drug anesthetics in lighter planes of anesthesia may contribute to prolonged laryngeal spasm.

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Influence of Music Upon Verbal Participation in Group Psychotherapy

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This experiment investigated the influence of background music upon verbal interaction during group psychotherapy. It studied the effect of music upon the quality and extent of participation in the group sessions.

Patients requiring socialization and group activity have often been encouraged to participate actively in music groups, e.g., humming groups, choral groups, rhythm groups, bands, or instrumental ensembles.[11] Group music appreciation classes have been employed to facilitate the psychotherapeutic treatment of patients[4,6,7,12] by providing a stimulus to group discussion. Color, motion, and music have been combined as "Auroratone" films to render depressed patients more open to group psychotherapy.[8] It has been demonstrated experimentally that music patterns can alter the verbal and neuro-muscular output of mental patients.[1,9,10]

The present study provides a quantitative evaluation of music's power to facilitate group psychotherapy by its influence upon verbal interaction when supplied as background to group psychotherapeutic discussions.

The following hypotheses were investigated:

1. a. That background music supplied during group psychotherapy significantly alters the group's frequency of verbal interaction;
   b. That it alters the quality of the verbal interaction.
2. a. That contrasted types of background music exert contrasted or differential influence upon the frequency of verbal interaction;
   b. These contrasted types of music exert a differential influence upon the quality of the verbal interaction.

Subjects

These were hospitalized male psychiatric patients who met three times weekly in group psychotherapeutic sessions of 45 minutes each. This was an ongoing group which had been meeting prior to this study and which continued to meet after its completion. Two clinical psychologists met with the group, one in the capacity of leader and the other as observer. They had been known to the patients in these same roles prior to the beginning of the experiment.

The median number of patients in attendance at group sessions was 11, with Q_1=10 and Q_3=12. The median age of the group was 30.5 years, Q_1=25 years and Q_3=35 years. The median educational level was 11th grade, Q_1=9th grade and Q_3=12th. The majority of these patients had held unskilled or semi-skilled positions; a small number came from clerical and white-collar occupations.

All were recent admissions, in good reality-contact, and without active psychosis. Their prognosis for the immediate future was at least fair. Their maximum length of stay, this hospitalization, was usually under six months. Although many carried schizophrenic diagnoses, their level of functioning was well outside the realm of psychosis. Diagnostically, the 48 patients who participated in this study were classified as follows: schizophrenic reaction 38%, personality disorder 24%, depressive reaction 19%, chronic brain syndrome 2%, and psychoneurosis 17%. The schizophrenic and the depressive reactions were in remission, and less severe than might be implied by their diagnoses.

The membership of the psychotherapeutic group was a changing one. Patients were intermittently discharged and replaced by others more recently admitted. The frequency of replacement was one or two patients weekly. A total of 48 patients participated in this study. Their median number of sessions attended was 9; Q_1=4 sessions and Q_3=19 sessions. The continuing core of the group was therefore quite stable, but from a long-term perspective there was fairly complete turnover of members over the course of the months.

All group members were also in individual therapy but not with the group leader. The

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leader took a neutral-to-supportive role in the group sessions. He attempted to define and to clarify issues; he stimulated discussion when it lagged; he led the members to psychological exploration of their behavior. The leader's role was flexible rather than rigidly defined, but he did avoid a dominating or didactic structuring of the meetings. The meetings had but two restraining rules: members could not use physical violence in the sessions, nor were they permitted to discuss group content with others outside the group.

These patients lived together upon the same wards, therefore they knew each other personally and interacted in many areas beyond the confines of the group sessions. Their attendance at group psychotherapy, as with all their therapies, was obligatory.

Experimental Stimuli

The group psychotherapeutic sessions were held in a conference room with all participants seated about a large conference table. Three experimental conditions were applied.

a. *No Music (Baseline).* This was the basal or control condition. It signified the absence of music from the meeting room during the session. The usual extraneous noises were present.

b. *Stimulating Music.* This was recorded on tape and supplied uninterruptedly and with good fidelity by a machine in one corner of the meeting room. Its sound volume, together with that of the Quieting Music discussed below, was maintained at a constant level. The Stimulating Music was selected according to the list of Skelly and Haslerud.[10] These authors had developed a gradient of music which ranged from stimulating at the one extreme to quieting and depressing at the other. Our Stimulating Music stimuli included the first ten stimulating selections listed by Skelly and Haslerud[10] (Table 1), and other pieces matched to this quality such as Coates' Knightsbridge March, Mayfair Valse, and Covent Garden Tarantelle; Kreisler's Tamborin Chinois, Liebesfreud, Schon Rosmarin, and La Gitana; Strauss' Tik-Tak Polka and Vienna Bon-Bon Waltz; and De Falla's Danza Espanola.

It was necessary to add selections matched to Skelly and Haslerud's list, both for Stimulating Music and for the Quieting Music described below in order to avoid excessive repetition of the same numbers.

c. *Quieting Music.* This was prepared and presented to the group as described above for Stimulating Music. The pieces came from the quieting portion of Skelly and Haslerud's list, but excluded the most extreme type of music which they had described as "depressing" or "dismal" (e.g., Barcarolle—Tales of Hoffmann by Offenbach; Sea Murmurs by Castelnuovo - Tedesco - Heifetz). It included additional matched selections such as Tchaikowsky's Andante Cantabile (from Quartet in D); Coates' Westminster; Kreisler's Liebeslied; Chopin's Waltz in C# Minor; and Serradell's La Golondrina (organ).

Sequence of Conditions

Each of the three conditions was presented for a series of four sessions. The conditions were rotated in series of four sessions each, according to the following design; *a* designates No Music, *b* Quieting Music, and *c* Stimulating Music: *a b a c, a c a b, a b a c, a.* There were 52 sessions in all—28 of No Music, 12 of Quieting, and 12 of Stimulating Music. It was sometimes necessary to hold the experiment in abeyance for one or more sessions, due to external factors such as special recreational event for the patients, breakdown in tape machine, absence of the observer, or absence of the leader. The experiment was always resumed as soon as possible, and at the appropriate point within the experimental design.

Categories of Measurement

Every verbalization by a group member or by the leader at each session was rated 1, 2, 3, or 4, according to a 4-step gradient ranging from positive, warm, and accepting at 1 to negative, hostile, and rejecting at 4. This scale was based upon Fine's adaptation[3,13] of Bales' Interaction Recorder and Gorlow's theme analysis..[2,5] The full scale, its scoring, and its reliability have been reported by Fine. Its scoring reliability was sufficiently accurate for our purpose.[3,13]

The ratings were made by the psychologist-observer, who had considerable preliminary training in the reliable application of this rating method. The observer did not

participate as a member of the meeting itself. The four rating steps are listed below. A score for silence (absence of verbalization) was included. This category, silence, received a unit score for every thirty seconds of duration. Thus, a silence which endured for 90 seconds received three such unit scores.

Scale

RATING 1—*Positive.* Expresses warmth, understanding, sympathy; accepts other's viewpoint. May include the asking of open-ended questions or the stating of tentative hypotheses.

RATING 2—*Neutral-to-Positive.* Expresses reassurance; gives information. May include requests for further information.

RATING 3—*Neutral-to-Negative.* Expresses counter opinion; confronts with inconsistencies or with weight of authority. May include persuading, advising behavior.

RATING 4—*Negative.* Openly hostile, rejecting; disapproves; deflates other's status.

CATEGORY SILENCES: A period of total silence lasting 30 seconds. Each multiple of 30 seconds is an additional unit of silence.

Every verbalization, whether of few or many words, was considered as a unit and rated holistically in terms of content, gesture, inflection, and modulation of voice. The observer began his ratings exactly five minutes after the session's official opening in order to allow for latecomers. Ratings were terminated at the close of the session 40 minutes later.

These ratings yielded two measurements which were employed to resolve the hypotheses posed earlier in this paper. One measurement pertained to the frequency of verbal interaction or participation. Each rating *per se* represented a verbal communication; a frequency count of these ratings was therefore a frequency count of the number of verbal participations.

The second measurement pertained to the qualitative feeling-tone of the verbalization: its place within the 4-step scale of positive acceptance—negative rejection, and its proportionate shift up or down that scale as the experimental conditions were varied.

In all instances the group members' participations were computed and evaluated separately from those of the leader.

Results

1. Influence on degree of group participation.

The mean frequency of verbalizations per session per group member was calculated under each condition and is reported in Table 1.

TABLE 1

Mean Frequency of Participation Per Group Member Per Session: Comparison Among the Three Conditions.

Conditions Compared	Mean Member Participations	p
Quieting Music	7.19	
vs.		.05*
Stimulating Music	9.57	
Quieting Music	7.19	
vs.		—
No Music	8.58	
Stimulating Music	9.57	
vs.		—
No Music	8.58	

*Statistically significant difference at the indicated confidence level.

Table 1 reflects a consistent increase in mean frequency of verbalization, from Quieting Music to No Music to Stimulating Music. This differential influence of Stimulating as against Quieting Music is statistically significant ($p=.05$). It is therefore concluded that Stimulating Music raises the mean frequency of participation over that of the basal condition No Music, while Quieting Music reduces it below the basal No Music.

The mean silence score was calculated for each experimental condition. The mean number of silence units per group member per session was, for each condition: Quieting Music=.99 units, No Music=.61 units, Stimulating Music=.45 units. This was reciprocal with the frequency of participation reported above, and logically consistent with it. The frequencies of participation under the several conditions stood in the order: Stimulating Music>No Music>Quieting Music; the frequencies of silence stood in the reverse order: Quieting Music>No Music>Stimulating Music.

Figure 1 portrays graphically the relative

frequencies of participation, and of silence, under the three contrasted conditions. The differential effects of these three conditions are manifest.

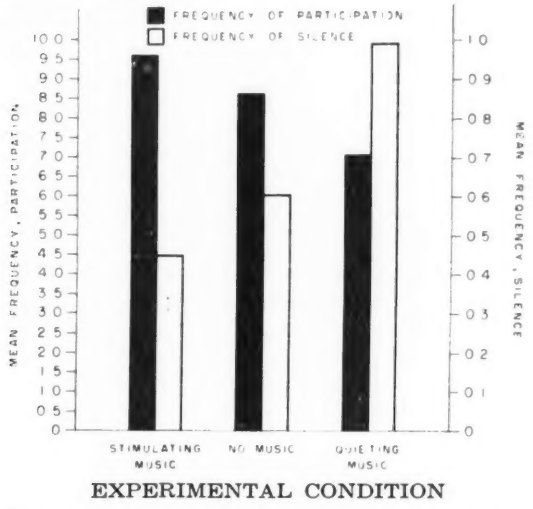

Fig. 1. Frequencies of participation and of silence under the three experimental conditions.

2. Influence on quality of group participation.

It will be recalled that each verbalization by a group member received a rating of 1 through 4 depending upon its positive and accepting or negative and rejecting quality. The total number of ratings within each of the four categories (1, 2, 3, 4) was computed for all sessions under each of the three conditions. In this way the frequencies and the relative proportions of 1:2:3:4-ratings were ascertained for each of the three respective conditions. The frequencies among the four rating categories under each condition, together with their relative proportions, are reported in Table 2.

The relative proportions among the four rating categories under each condition are graphically illustrated in Figure 2. The contrasts are evident.

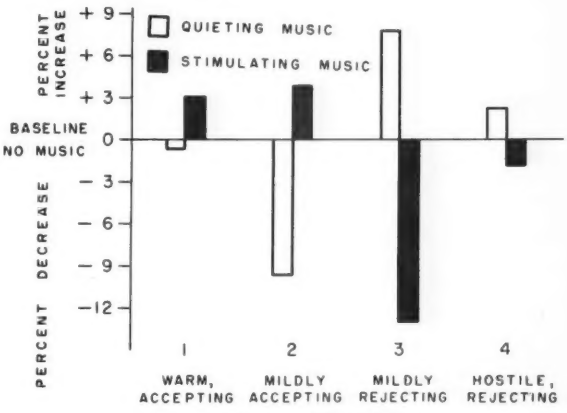

Fig. 2. Quality of group's response. Percentage of increase or decrease in each rating category for *Quieting* and *Stimulating Music* respectively, compared with *No Music* (baseline).

The statistical significance of these shifts in the proportions of the cognate ratings from condition to condition was tested by Chi Square. Quieting Music was tested against No Music, Stimulating Music against No Music, and Quieting Music against Stimulating Music. In every test, the difference in proportions among the four rating steps was statistically significant at the $p<.001$ confidence level. The shifts in response to each condition were unequivocally significant.

Where a Music condition was tested against No Music, the former was always taken as the observed frequency and the latter as the theoretical frequency. Where Quieting Music was tested against Stimulating Music, the former was taken as the theoretical frequency and the latter as the observed.

Quieting Music evoked a significantly higher proportion of hostile and negative responses than did No Music, whereas Stimulating Music evoked a significantly lower proportion of such responses. Conversely, Stimulating Music effected a significantly higher proportion of positive, warm and

TABLE 2

Quality of Group Participation in Response to the Three Experimental Conditions.

RATING	CONDITION					
	Quieting Music		No Music		Stimulating Music	
	No.	%	No.	%	No.	%
1—Warm, Accepting	75	6.9	200	7.5	112	10.6
2—Mildly Accepting	280	25.9	948	35.5	417	39.4
3—Mildly Rejecting	657	60.8	1412	52.9	506	47.8
4—Hostile, Rejecting	68	6.3	105	4.1	23	2.2
Grand Totals	1080	100%	2667	100%	1058	100%

accepting responses than did No Music, whereas Quieting Music evoked significantly lower ratio of such responses. It was apparent that Quieting Music shifted the response ratio toward the hostile portion of the scale; Stimulating Music, toward the warm and friendly portion. These shifts occurred over the full four steps of the scale; they were not merely confined to one or two of the steps. Chi Square analyses of the shifts within each one of the four steps made this quite apparent.

It must be concluded that Quieting and Stimulating Music exert significant but contrasting effects upon the quality of the group's participation.

3. Response of leader.

The influence of the three respective experimental conditions upon the leader's participation was analyzed by the same methods employed for the group's participation.

a. Frequency of participation.

Results were generally similar to those for the group members. The leader participated significantly more often under Stimulating Music than under No Music ($p=.05$) or under Quieting Music ($p=.01$).

b. Quality of participation.

The differential qualitative alterations in the leader's verbalizations evoked by the three experimental conditions (see Figure 3) were fully congruent with those induced in the group (Figure 2). Chi Square tests were conducted. Stimulating Music caused a statistically significant shift in ratings toward the direction of 1 (warmth, acceptance) when compared with the baseline No Music ($p=.05$), while Quieting Music evoked a significant shift toward 4 (hostility, rejection) ($p=.05$).

The relationship between type of music (Stimulating versus Quieting) and direction of shift was again statistically significant at the $P<.001$ confidence level. Stimulating Music caused displacement toward the rating of 1 while Quieting Music forced a displacement toward 4.

c. Relationship between group's and leader's response.

It might have been argued that the group's differential responsiveness to the three experimental conditions was merely a reflection of the leader's differential responsiveness. The leader could be by definition a most powerful influence upon the group, and hence upon participation. It was therefore necessary to evaluate this leadership influence as a possible explanation for the group's different reaction to each of the three experimental conditions.

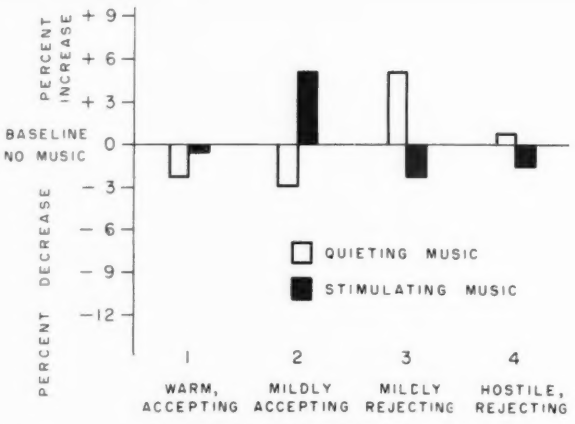

Fig. 3. Quality of leader's response. Percentage of increase or decrease in each rating category for *Quieting* and *Stimulating Music* respectively, compared with *No Music* (baseline).

Did the leader exert such an influence upon the group's degree and type of participation, then within each condition there should have been a significant correlation between the group's response and the leader's response from session to session. A rank order correlation (RHO) was therefore computed between group's and leader's frequency of response for the twelve sessions under Quieting Music. The correlation was negligible. An equivalent RHO was also computed for the quality (mean ratings) of participation over the twelve sessions. Again the correlation was negligible. Similar rank order correlations were computed for the twelve sessions under the condition Stimulating Music. These too were negligible. None of the RHO's gave the slightest evidence of any relationship between quality or quantity of the leader's participation and quality or quantity of the group's participation. Finally, Chi Square tests of independence were conducted for the quantity and the quality of participation respectively by group and by leader under the condition of No Music ($N=28$ sessions). The Chi Squares were in-

significant; the hypotheses of independence were therefore retained.

To summarize, there was no evidence of any association between the participation of the group and that of the leader: either in quality or in frequency of verbalization. In the absence of any such demonstrable correlation, there is no reason to believe that the leader's participation did influence that of the group. Therefore, the group's differential reaction to the three respective experimental conditions is not merely a reflection of the leader's differential reaction to those conditions, but constitutes a true differential response to each of those conditions. Although the influence of the conditions upon the group is similar to that upon the leader, that influence is exerted independently. There is no causal relationship.

Discussion

The similarity of response between group and leader argues for the lawfulness of these findings. This was actually an experimental replication from group to leader, and equivalent results were obtained in each case.

Both hypotheses posed earlier are now answered in the affirmative: (1) Background music does significantly alter the frequency and quality of verbal interaction during group psychotherapy when compared to No Music, and (2) Contrasted types of background music do exert a decidedly differential influence upon verbal interaction (quality and frequency) during group psychotherapy.

Frequency of participation may be reasonably taken as an index of group cohesion, with greater frequency indicating greater cohesion. Quality of participation may also be taken as a cohesion index, with positive ratings (or 1) indicating greater cohesion and negative ratings (or 4) indicating lesser cohesion. Stimulating Music promoted greater group cohesion according to both these criteria, while Quieting Music induced group disruption by these same criteria.

These results do not mean that Stimulating Music is invariably preferable to Quieting Music during group psychotherapy. Should it be desired to decrease the frequency of verbal interaction, as in a group with excessive frequency of verbal interchange, then Quieting Music might be the music of choice. Should it be desired to encourage hostile, angry, or negative interaction, as when a group is "on its good behavior" and will not voice negative or depth expressions of feeling, then Quieting Music might again be the music of choice.

The present findings are limited to the subject population utilized in this study. This experiment requires extension to other patient populations. Will these contrasted types of music, Stimulating and Quieting as defined in the present investigation, yield similar results (to this study) when applied to patient populations which ordinarily show very little verbal interaction? Or, when applied to populations which ordinarily show a high frequency of verbal interaction? Are the findings, again, similar when the subject population's verbalizations are ordinarily highly positive? Or, when they are usually very negative? The interaction of subject sample type with music stimulus must be ascertained by the study of a wide variety of subjects or patients.

Three additional lines of investigation hold pragmatic value for group psychotherapy: (a) Does background music during the group session influence the subjective time estimate of the speed with which that hour or session passes? (b) Does background music render the group psychotherapy sessions more attractive, thereby decreasing patient absences where attendance is voluntary? (c) Can background music be used to enhance group cohesion during the early sessions of a newly formed psychotherapeutic group?

Although we found no correlation between the group's and the leader's participation, this does not mean that there are no relationships at all. It means simply that for these patients under the circumstances of this group therapy and these leadership techniques, there is no correlation between leader's response and group's response for the two indices studied.

Music *per se* is not a distracting influence to group psychotherapy, as evidenced by the increased frequency of verbally participative interaction under Stimulating Music. The patients themselves made no complaints

about music as distraction, although they were well aware of the presence of music. Several comments were made to the effect that music was desirable during sessions where there were long or frequent silences.

The results of this study suggest that music may provide an impersonal modality for control of the quality and degree of verbal interaction during group psychotherapy: impersonal in that its influence is exerted through a mechanical medium and independently of the group leader's behavior.

Summary

The influence of background music upon the quantity and quality of verbal interaction during group psychotherapy was studied. Three experimental conditions were employed in the design: Quieting Music, No Music and Stimulating Music. There were 52 sessions in total.

Every verbalization was rated on a 4-step scale, from positive and sympathetic at 1 to negative and hostile at 4. The quantum of silence during the session was measured, too. The group members' participation was analyzed separate from that of the leader.

The group showed a consistent mean increase in frequency of verbalization, from Quieting Music to No Music to Stimulating Music (Quieting Music vs. Stimulating Music—p.=.05). The amount of silence was measured, and this stood in the reverse order: more silence under Quieting Music, less under No Music, and least under Stimulating Music. This reciprocal relationship of silence with participative frequency was logically consistent.

The group's quality of participation under the three conditions was measured by the relative frequencies among the four ratings under each condition. The differences in the relative proportions of 1-, 2-, 3-, and 4-ratings between Quieting Music, No Music, and Stimulating Music respectively were tested by Chi Square for statistical significance. The relative frequencies showed a decidedly significant shift in every instance ($p<.001$) from greatest emphasis upon the positive-sympathetic ratings under Stimulating Musim, to greatest emphasis upon negative-hostile ratings under Quieting Music.

Analysis of the leader's responses under the several conditions gave very similar results to those for the group, both in frequency and quality of participation. The hypothesis was statistically tested that the group's qualitative and quantitative response was causally related to or dependent upon the leader's response. This was rejected. The results for group and for leader were equivalent, but independent of each other.

The significance of these findings was discussed, and future lines of investigation suggested. It was concluded that background music supplied during group psychotherapy can alter the frequency and quality of participation; and that contrasted types of background music can exert contrasted or differential effects in this regard.

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Acetylcarbromal and Bromisovalum in Combination

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In a previous clinical report[1] it has been shown that two monoureide sedatives, namely acetylcarbromal and bromisovalum, are never habit forming; also, that their continued use shows no toxic or untoward effects. The present paper deals with therapeutic results from the standpoint of efficacy as a sedative and somnifacient. We believe that the comparative studies herein reported have established a definite synergism between acetylcarbromal and bromisovalum. This combination proved more effective therapeutically than double doses of either acetylcarbromal or bromisovalum used singly. In fact, in the daily recommended dosage of 5 tablets it was found to be equivalent to phenobarbital ½ grain in sedative potency, minus the serious toxic and habituating effects of that drug.

Our studies further confirmed statements in the literature that acetylcarbromal and bromisovalum, when used singly, are too weak to provide reliable sedative and somnifacient effects. Thus Goodman and Gilman[2] write: "The clinical use of monoureides has been somewhat disappointing due to their feeble depressant effects." Of carbromal the United States Dispensatory[3] says that being a monoureide, "it is a feeble hypnotic and sedative." The desirability of combining carbromal or its derivative, acetylcarbromal, with another sedative is suggested by the following statement:[3] "Carbromal, in sufficient dose, possesses some somnifacient effect and is used in mild sleeplessness, often in combination with another central nervous system depressant." Cook and Martin[4] describe carbromal, the parent substance of both acetylcarbromal and bromisovalum, as follows: "Carbromal is a weak hypnotic and is but infrequently used in modern therapeutics. . . . Due to its feeble central depressant effects, its action is often unreliable and disappointing." Sollmann[5] writes that bromural (bromisovalum) "is a prompt but mild hypnotic, effective only in slight nervous insomnias."

Synergistic Combination

In his discussion of synergists, Grollman[6] says that "the presence of another drug having the same effects in the body often increases the action of a remedy to an unexpected extent. This is the ground for the prescription of several remedies acting in the same way." He adds that "in some cases the increased activity of one drug in the presence of another is remarkable." In mentioning drug combinations Goodman and Gilman[7] write: "There are instances in which the combined action of two drugs is greater than that which can be anticipated from the sum of their individual actions. This is known as *potentiation.*"

The definition of synergism between two drugs of like action given by Bastedo[8] is as follows: "*Synergism* is the production by two or more like drugs of effects beyond the sum of the effects of the individual drugs. . . . As might be surmised, the same dose of a drug will exert its usual form of activity more easily if given with other drugs of the same class; and a combination of two similar drugs may gain a result that one alone will not give in any dose." The synergism which we have found to exist between acetylcarbromal and bromisovalum comes within Bastedo's specific definition.

Clinical Investigation

The series of 50 nervous patients used for comparison of acetylcarbromal, bromisovalum and the acetylcarbromal-bromisovalum combination included 38 cases of anxiety state and 12 of extreme nervousness. There were 34 females and 16 males in ages ranging from 18 to 70, average 49. Weights ranged from 108 to 230 lb., average 150 lb.; heights from 62 to 73 in., average 66 in.

The fifty patients with anxiety state or extreme nervousness were treated with each of the following drugs for three successive periods of two months, six months in all:

Acetylcarbromal 300 mg., 6 tablets daily

as a sedative, 8 tablets daily as a somnifacient.

Bromisovalum 200 mg., 6 tablets daily as a sedative, 8 tablets daily as a somnifacient.

Acetylcarbromal 150 mg. combined with bromisovalum 100 mg., 6 tablets daily as a sedative, 8 tablets daily as a somnifacient.

It is to be noted that the amount of the drug used singly was twice that in the combination. All tablets of the different compounds had the same appearance, so as to eliminate any psychological influence.

The three groups were alternated with reference to the order of medication used. Thus one group started with bromisovalum for the first two months, changed to acetylcarbromal for the second two months, and finished with acetylcarbromal-bromisovalum combination for the third two months. Another group started with acetylcarbromal for the first two months, changed to acetylcarbromal-bromisovalum combination for the second two months, and finished with bromisovalum for the third two months. A third group started with acetylcarbromal-bromisovalum for the first two months, changed to bromisovalum for the second two months, and finished with acetylcarbromal for the third two months. Subsequent cases of the series were scheduled with this same order of alternation.

In 50 cases including the symptoms of nervousness, anxiety and insomnia, the comparative therapeutic results were as shown in Table 1.

A good therapeutic result with the acetylcarbromal-bromisovalum combination was obtained in 31 cases (62%) as compared with 23 cases (46%) for acetylcarbromal and 14 cases (28%) for bromisovalum.

A fair therapeutic result with the acetylcarbromal-bromisovalum combination was obtained in 15 cases (30%), in addition to the 62% good results, as compared with 21 cases (42%) for acetylcarbromal and 25 cases (50%) for bromisovalum.

A poor result with the acetylcarbromal-bromisovalum combination was obtained in 4 cases (8%) as compared with 6 cases (12%) for acetylcarbromal and 11 cases (22%) for bromisovalum.

Table 2 summarizes the comparative results in terms of the individual symptoms.

In 25 cases of insomnia, the comparative results covering somnifacient efficacy were as follows:

A good therapeutic result with the acetylcarbromal-bromisovalum combination was

TABLE 1

Comparative Therapeutic Results in 50 Cases

Daily 6 tablets as sedative, 8 tablets as somnifacient

Drug	RESULTS Good	Fair	Poor
Acetylcarbromal 300 mg.	23 (46%)	21 (42%)	6 (12%)
Bromisovalum 200 mg.	14 (28%)	25 (50%)	11 (22%)
Acetylcarbromal 150 mg. + Bromisovalum 100 mg.	31 (62%)	15 (30%)	4 (8%)

TABLE 2

Comparative Relief of Symptoms in Series of 50 Cases

(6 tablets daily as sedative, 8 tablets daily as somnifacient)

		Acetylcarbromal 150 mg. + Bromisovalum 100 mg.		Acetylcarbromal 300 mg.		Bromisovalum 200 mg.	
Insomnia (25 cases)	good	15	(60%)	9	(36%)	8	(32%)
	fair	8	(32%)	13	(52%)	14	(56%)
	poor	2	(8%)	3	(12%)	3	(12%)
Tremor (37 cases)	good	25	(68%)	16	(43%)	9	(24%)
	fair	4	(11%)	7	(19%)	9	(24%)
	poor	8	(22%)	14	(38%)	19	(51%)
Muscular Relaxant (50 cases)	good	26	(52%)	19	(38%)	12	(24%)
	fair	15	(30%)	14	(28%)	13	(26%)
	poor	9	(18%)	17	(34%)	25	(50%)
Hysteria (50 cases)	good	29	(58%)	22	(44%)	13	(26%)
	fair	11	(22%)	10	(20%)	10	(20%)
	poor	10	(20%)	18	(36%)	27	(54%)

obtained in 15 cases (60%) as compared with 9 cases (36%) for acetylcarbromal and 8 cases (32%) for bromisovalum.

A fair therapeutic result with the acetylcarbromal-bromisovalum combination was obtained in 8 cases (32%), in addition to the 60% good results, as compared with 13 cases (52%) for acetylcarbromal and 14 cases (56%) for bromisovalum.

A poor therapeutic result with the acetylcarbromal-bromisovalum combination was obtained in two cases (8%) as compared with three cases each (12%) for acetylcarbromal and bromisovalum.

Tremor was present in 37 cases. The acetylcarbromal-bromisovalum combination relieved this symptom completely in 25 cases (68%), partially in 4 additional cases (11%), no relief in 8 cases (22%). Acetylcarbromal relieved tremor completely in 16 cases (43%), partially in 7 additional cases (19%), no relief in 14 cases (38%). Bromisovalum relieved tremor completely in 9 cases (24%), partially in 9 additional cases (24%), no relief in 19 cases (51%).

The value of the medication to produce muscular relaxation was studied in 50 cases. The acetylcarbromal-bromisovalum combination produced complete muscular relaxation in 26 cases (52%), partial relaxation in 15 additional cases (30%), no relaxation in 9 cases (18%). Acetylcarbromal produced complete muscular relaxation in 19 cases (38%), partial relaxation in 14 additional cases (28%), no relaxation in 17 cases (34%). Bromisovalum produced complete muscular relaxation in 12 cases (24%), partial relaxation in 13 additional cases (26%), no relaxation in 25 cases (50%).

Absence or impairment of the gag or corneal reflexes is one of the signs of hysteria. Restoration or improvement of these reflexes is an indication of recovery. Either or both of these reflexes were absent or impaired in 50 cases. The acetylcarbromal-bromisovalum combination restored these reflexes completely in 29 cases (58%), improved them in 11 additional cases (22%), no change in 10 cases (20%). Acetylcarbromal restored the reflexes completely in 22 cases (44%), improved them in 10 additional cases (20%), no change in 18 cases (36%). Bromisovalum restored the reflexes completely in 13 cases (26%), improved them in 10 additional cases (20%), no change in 27 cases (54%).

In summary, the acetylcarbromal-bromisovalum combination in comparison with double quantities of acetylcarbromal and bromisovalum used singly gave superior sedative and somnifacient results as a whole and also with respect to each of the individual symptoms studied. These results are evidence of synergism in that the therapeutic action of the combination was found to be increased beyond the additive actions of the two drugs.

Comparison With Phenobarbital

The monoureides (including carbromal, acetylcarbromal and bromisovalum) have been described as feeble sedatives. Our own studies have confirmed this fact with respect to acetylcarbromal and bromisovalum used individually. When acetylcarbromal and bromisovalum are combined in suitable proportions, however, there is a substantial increase in sedative and somnifacient efficiency. Because of this observation we made a comparison between the acetylcarbromal-bromisovalum combination and phenobarbital.

In a group of 23 patients suffering from nervousness and anxiety, the average effective doses of acetylcarbromal-bromisovalum combination and phenobarbital, respectively, were determined by comparative clinical study. It was found that an average daily dosage of 5 tablets each containing acetylcarbromal 150 mg. combined with bromisovalum 100 mg. was equivalent in therapeutic potency to the usual single dose of phenobarbital 30 mg. (USP XV[9]), divided into equal daytime and evening doses.

Case Histories

Case 1. R.D., age 44 years, height 66 inches, weight 135 pounds, female, complained of tenseness, emotional upsets and nervousness for the past 6 years. Physical examination was essentially noncontributory. The diagnosis was extreme nervousness. While taking bromisovalum (6 tablets per day) for 2 months, the patient still complained of nervousness. Tremor (small random movements) was still observable. The responses to the relaxation and hysteria tests showed no improvement. While taking acetylcarbromal (6 tablets per day) for 2 months the patient reported that she was less

nervous. Tremor was present. The responses to the relaxation test showed improvement but the responses to the hysteria tests remained constant. While taking the acetylcarbromal-bromisovalum combination (6 tablets per day) for 2 months the patient did not complain of nervousness. Tremor was not present. The responses to the relaxation and hysteria tests were good. There were no untoward effects while taking any of the medications described. The patient showed poor results from bromisovalum, fair results from acetylcarbromal, and good results from the acetylcarbromal-bromisovalum combination.

Case 2. E.D., age 25 years, height 63 inches, weight 116 pounds, female, complained of nervousness and fear for the past 2 years. Physical examination was essentially non-contributory. The diagnosis was extreme nervousness. While taking bromisovalum (6 tablets per day) for 2 months, the nervousness was slightly relieved. Tremor was still present. There were no changes in her responses to the relaxation and hysteria tests. While taking acetylcarbromal (6 tablets per day) for 2 months the patient reported that she was less nervous. Tremor was not present. There were no changes in her responses to the relaxation and hysteria tests.

While taking the acetylcarbromal-bromisovalum combination (6 tablets per day) for 2 months the patient revealed that she was less nervous. Tremor was not present. Patient showed good relaxation and the gag and corneal reflexes were intact. There were no untoward effects with any of the medications. The patient had a fair result from bromisovalum and acetylcarbromal, and a good result from the acetylcarbromal-bromisovalum combination.

Case 3. H.G., age 43 years, height 66 inches, weight 135 pounds, female, complained of insomnia, nervousness, and anxiety for the past 3 years. Physical examination was essentially non-contributory. The diagnosis was anxiety state.

While taking bromisovalum (8 tablets per day) for 2 months, the nervousness and anxiety were slightly relieved. Insomnia was somewhat relieved. Tremor was present. There was some improvement in the responses to the relaxation and hysteria tests. While taking acetylcarbromal (8 tablets per day) for 2 months, the patient reported that nervousness and anxiety were slightly relieved. Insomnia was somewhat relieved. Tremor was present. There was some improvement in the responses to the relaxation and hysteria tests. While taking the acetylcarbromal-bromisovalum combination (8 tablets per day) for 2 months, the patient revealed that the nervousness and anxiety were completely relieved. Insomnia was no longer present. Tremor was not present. There was some improvement in the response to the relaxation test and good responses to the hysteria tests. There were no untoward effects with any of the medications. The patient had a fair result from bromisovalum, with insomnia fairly well controlled, a fair result from acetylcarbromal with insomnia fairly well controlled, and a good result from the acetylcarbromal-bromisovalum combination with insomnia well controlled.

Conclusions

1. Acetylcarbromal and bromisovalum are safe and non-habituating sedatives and hypnotics. Their therapeutic action, however, when used singly, is feeble and often unreliable.

2. There is a definite synergism between acetylcarbromal and bromisovalum, with the result that a combination of these two drugs in suitable proportions provides satisfactory results as a daytime sedative and somnifacient.

3. A daily dosage of 5 tablets containing acetylcarbromal 150 mg. in combination with bromisovalum 100 mg. was found to be equivalent to a daily dosage of ½ grain of phenobarbital, minus the serious toxic and habituating effects of that drug.

4. The use of this acetylcarbromal-bromisovalum combination is recommended instead of the barbiturates, particularly in cases where administration of a sedative or somnifacient must be continued.

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Authors' Note: The combination of drugs used in this study was supplied as Sedayson tablets by Tailby-Nason Co., Inc., Dover, Del. Each tablet contains acetylcarbromal 150 mg. and bromisovalum 100 mg.

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Eastern Psychiatric Research Association

ELEVENTH SCIENTIFIC MEETING*

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Psychiatric Aspects of Multiple Sclerosis

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Psychiatric changes in multiple sclerosis are mentioned in virtually all descriptions of the disease. A survey of the literature on this subject, however, shows that there is no unanimity as to the nature of the psychiatric pathology.

An interesting illustration of the divergence of findings and opinions is provided by comparison of the papers and discussions at the Association for Research in Nervous and Mental Diseases which discussed multiple sclerosis in 1922 and again in 1950. In the 1922 discussion, Brown and Davis mentioned the incidence of mental symptoms as being 90%. In 1950, Langworthy found that one out of every twelve cases of multiple sceloris required psychiatric hospitalization. Brown and Davis described euphoria, occasionally reaching a manic-like state, and depression as the most frequently encountered symptoms. They considered euphoria as a primary symptom resulting from organic changes in the brain; that depression was not of the same origin but rather a secondary psychological reaction to the disease. In 1950, Braceland and Giffin found that only a small number of their patients could be characterized as euphoric, whereas a slightly larger group presented depression. The largest group reacted to their illness with moods commensurate with their conception of the probable outlook for their future. Braceland and Giffin found that all patients who exhibited euphoria showed evidence of widespread cerebral disease. These authors believed that the euphoria represented an affective defense reaction designed to maintain psychological homeostasis. Most of the patients reacted with a normal degree of anxiety and concern consistent with the degree of their disability. Braceland and Giffin postulated that the emotional reactions of patients varied, not only in accordance with their own particular make-up, but also with the different stages of the illness. In the initial stage, the patient's premorbid latent conflicts are activated by the stress of the disease. In the late chronic stage, the mental changes may be the result of organic brain pathology. In all stages, the basic personality make-up may largely determine the psychiatric symptomatology, and the disease does not cause a specific charactereological imprint.

Carter, Sciarra and Merritt found objective evidence of mental changes in 61% of their cases; 52% showed affective disturbances; deterioration was seen in 26% and psychotic manifestations in 4%. Amongst the affective disturbances euphoria predominated in their series. Harrower found that psychometric and personality tests showed patients with multiple sclerosis to be characterized by exaggerated submission, compliance and absence of inner tension. Resignation and acceptance appeared to be outstanding features. In the discussion, Mackay painted out that he never had seen a patient with multiple sclerosis who, clinically speaking, could be said to be euphoric. His statement contradicts a study by Cottrell and Wilson who, in 1926, published a survey of the affective symptomatology of 100 cases of multiple sclerosis. They not only stressed the frequency of occurrence of euphoria sclerotica as a very common affective state in which the prevailing mood is one of serenity and cheerfulness, but they also differentiated it from eutonia sclerotica which they found in many patients who were conscious of a feeling of bodily health and of feeling fit and tuned up and at the same time not aware of their physical disability. Cottrell and Wilson attached fundamental significance to eutonia sclerotica present in the majority of their patients, while only a small percentage expressed any sense of physical illness. In addition to change in mood and change in bodily feeling, these authors stressed the exaggeration of emotional expression which they found in almost all cases. They did not identify the pronounced facility for exaggeration of emotional expression with forced laughter or crying. They also stressed the optimistic outlook of patients with multiple sclerosis (spes sclerotica). Cottrell and Wilson felt that eutonia, euphoria and exaggeration of emotional expression were direct results of the disease process and completely independent of duration, degree or clinical type. According to their observations, these features were more frequent than any single neurological symptom and constituted a diagnostic triad of greater value than any neurological symptom complex. They associated the involvement of the affective sphere with the periventricular subependymal spread of the disease.

In 1950, I. Bender published an extensive study on mental changes in multiple sclerosis which, in her material, occurred in half of the cases. She stressed the subjective signs of well-being and a peculiar state of euphoria as characteristic symptoms, while she reported only rare incidences of dysphoria. Furthermore, she described intellectual disturbances and character changes as concomitant features. During the early stages of the disease, according to Bender, mood and affect are more involved, whereas in the later stages intellectual and character changes appear. Her anatomical findings pointed towards a relationship between involvement of the periventricular gray, hypothalamus and thal-

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amus with the psychiatric symptomatology. Numerous other authors (Lewy, Marburg, Spielmeyer, Ziehen, Redlich, Oppenheim, Runge) also have stated that cerebral sclerotic plaques in certain areas of the brain are responsible for the various psychiatric manifestations. Runge, who mentions depressions among other psychiatric changes, feels that reactive depressions are not rare but that in the advanced stages euphoria as well as depression are of organic origin.

Langworthy found manifestations of conversion hysteria and also the personality structure characteristic of conversion hysteria. Occasionally schizophrenic-like pictures have been described. (Duge, Osteman, Schuster, Moenkemoeller, Kraepelin, Marburg.) Ferraro described a case of a clinically typical picture of schizophrenia which on autopsy showed diffuse demyelinization of the brain. Geocaris, who reported four cases of psychotic syndromes in multiple sclerosis, found no correlation between the psychiatric and neurological disorder.

In the experience of the authors, affective derangements are the most frequently encountered psychiatric complications of multiple sclerosis. These derangements, however, are not of the type described by Cottrell and Wilson. The authors have seen euphoria polysclerotica in much rare instances than they have encountered depressive pictures. We have seen in the early stages of the disease an emotional state which is less characterized by an outspoken euphoric affect than by a bland state of indifference and absence of concern about the disability. This state reminded us of the indifference towards pain seen in lobotomies performed for the control of pain. It also resembles a similar absence of emotional responsiveness occasionally achieved by the varius phenothiazine derivatives. It may be assumed that this state of emotional indifference is due to anatomical involvement of the same structures which directly or indirectly are affected by lobotomy or those affected by drugs. Less frequently, the same changes have been observed in the late stages of the disease.

Depressive syndromes are the most frequently encountered psychiatric complications. These depressive manifestations vary in type but do not appear to have convincing characteristics of an organic origin. Mostly they appear to be the logical and completely understandable psychological reaction of the patient to his disabled state and to the progression of the illness. The question arises why an organically caused state of bland indifference, as seen in the very early stages, should not continue or increase during the subsequent course of the disease but should rather be substituted for by a non-organic psychogenic depressive syndrome. The only answer which could be given would be to assume that the psychological impact of the increasing disability, combined with the gradual realization of the usually poor prognosis, outweighs the comparatively mild organically induced indifference.

Depressive reactions may be explained by the actual disability, or be associated with neurotic overawareness and over-emphasis of factually minor physical symptoms; more often they are due to anticipated symptoms, in other words, the patient's knowledge of his diagnosis and prognosis. Probably in the majority of cases both types of depressive mechanisms are present simultaneously and will not only overlap but be mutually aggravating. It can be easily understood that the severe incapacitation frequently encountered, particularly during the later stages, causes severe depressive reactions. Naturally, sphincteric involvement will have an even greater impact than disturbance of motor power and coordination. However, involvement of the latter alone is frequently vastly sufficient to cause depressive reactions, particularly when it forces cessation of work and, in the breadwinner, may mean financial ruin for the entire family. Sphincteric involvement means final cessation of sexual activity which otherwise is in many instances continued into a fairly late stage of the disease. In female patients who fear progressive estrangement from their husbands on whom, by virtue of their disease, they have become extremely dependent sphincteric disturbances may act as an excessively severe psychic trauma.

In addition to the actual incapacitation, neurotic over-awareness and concern with regard to the physical symptoms is linked to depressive reactions. One of our patients, a premorbidly anxious, neurotic individual, stated clearly that about 80% of her motor power and coordination in her lower extremities was retained when she was alone and not observed, but that only 5% was left when she felt that others were watching her. She was able to walk well and unassisted when alone, but in the presence of relatives or acquaintances she stumbled and fell frequently. Awareness of the diagnosis and its prognostic implications may act as a psychological trauma on a patient who, prior to his knowledge of the diagnosis, may not have shown psychological repercussions to his physical disability. A patient, moderately incapacitated by the organic disease process, may develop a superimposed psychogenic depression as well as additional psychogenic impairment of somatic functions under the psychic trauma of knowledge of the diagnosis. This is illustrated by the following cases.

Case 1. A 28-year old married woman school teacher was seen 3½ years after onset of multiple sclerosis. There had been a two-year period of remission shortly after onset. After this remission, the patient developed difficulties in walking which, however, were not advanced enough to interfere seriously with her functioning as wife and school teacher. She had read about the opening of a multiple sclerosis clinic in a magazine article which enabled her to arrive at the proper diagnosis of her condition. This resulted in a severe state of depression with a psychogenic inability to walk and in her complete withdrawal from all activities. Some of her statements read as follows: ". . . the description of people in the wheel chairs—all it does, it makes me cry. I was fine until I found out by reading an article on the dedication of this clinic at Bellevue." This patient showed only a limited response to intensive psychotherapy and after six months of psychotherapy still had suicidal ideas. She had returned to her teaching job only for three

days, but her depressed state, her fear of becoming a burden to her husband and of having to be put into a home did not allow her to resume her former activities.

Case 2. A 38-year old widow had been sent to a hospital for complete neurological work-up to confirm the previously made diagnosis of multiple sclerosis which had not been revealed to the patient before she entered the hospital. When she visited the examiner's office after discharge and confirmation of the diagnosis, she was unable to walk and used a wheelchair. Neurological examination showed a clinical picture which did not satisfactorily explain the patient's inability to walk. The patient had become acquainted with the diagnosis, and apparently only the most unfavorable aspects of it had impressed themselves on her mind. After a psychotherapeutic interview of one hour, in which it was attempted to dispel her fears concerning the diagnosis, the patient left the office walking without assistance. Undoubtedly, her organic symptomatology had been overlaid by a psychogenic superstructure which in this case was easily removed.

Case 3. A young married woman, age 25, was seen in a state of complete remission. The patient was not physically incapacitated but was seriously depressed by the fact that she had multiple sclerosis. She and her husband had consulted medical text-books on the subject and had been impressed by the sinister aspects of the prognosis. On neurological examination for final confirmation of the diagnosis. They revealed that they had made a suicide pact which they intended to carry out once the diagnosis was confirmed.

The psychological impact of the knowledge of the diagnosis may occasionally be entirely out of proportion to the degree of physical incapacitation. A well functioning patient may become suicidal when he learns that he has multiple sclerosis.

That our material shows marked preponderance of depressive reactions whereas other authors report a preponderance of euphoria can probably be explained by the different nature of the material. Our patients were seen in private practice and were in early stages of the diseas. Other authors have chiefly studied permanently hospitalized, advanced cases. In the latter group organic changes associated with silly euphoria appear to be dominant.

Major psychoses in multiple sclerosis are not infrequent. The question arises whether such cases are a symptomatic organic reaction as seen, for instance, in infectious diseases, or whether they are an endogenous psychosis occurring more frequently in patients with this neurological disease. In the cases we saw, the symptomatology permitted differentiation from the fleeting episodes which have the characteristics of an organic reaction (symptomatic psychosis). The latter may have schizophreni-form characteristics but they do not develop into a lasting psychosis. Endogenous psychoses in patients with multiple sclerosis occurs when both illnesses manifest themselves independently. One of us had under observation three such cases almost simultaneously. The first case concerns an endogenous depression, the second and third schizophrenic psychoses, obviously unrelated to the multiple sclerosis.

Case 4. A 35-year old female developed the first symptoms of multiple sclerosis two months after the birth of her child. She became unsteady and had visual as well as sensory disturbances. Temporal pallor and a combination of pyramidal and cerebellar symptoms pointed to a diagnosis of multiple sclerosis. Three years after onset of these progressive symptoms to which she was able to adjust very well, she developed a depression. Her depressive ideas did not center around her illness but were severe enough to lead to a serious suicidal attempt. A series of eight electric shock treatments was given under which the depression cleared up. Also neurologically she functioned somewhat better. However, during the following three years the neurological symptoms progressed further, and the patient became unable to leave her house. The depression did not return, and the patient, though unhappy about her condition, continued to be a very active and responsible mother.

Case 5. This 31-year old female developed spastic paraparesis and other symptoms which indicated a diagnosis of multiple sclerosis. One year after onset she expressed the delusion of being hypnotized and subsequently went into a catatonic stupor. A diagnosis of schizophrenia was made and a series of 20 electric shock treatments were given. She responded temporarily but relapsed again and again given ECT. Her psychotic symptomatology and response to treatment did not differ from many other catatonic schizophrenics.

Case 6. This 33-year old female became unsteady on her feet. Ten months later she showed temporal pallor, right-sided hemiparesis, ataxic symptoms and other findings. A diagnosis of multiple sclerosis was made. She was seen again eight years later when her neurological symptoms were less pronounced but she showed a paranoid syndrome with various delusions for which she was treated successfully with ECT.

In none of these three cases had there been any evidence of an organic nature of the psychosis.

Short-lasting psychotic episodes during acute flare-ups of neurological manifestations are a known feature in multiple sclerosis, although the authors had no such cases in their own experience.

Aside from the short-lasting "symptomatic" organic psychoses due to the brain pathology of multiple sclerosis, there are progressive, permanent mental changes in advanced cases of the disease. They are characterized by general mental deterioration. In these cases a silly euphoria, so much discussed in the literature, is a frequent symptom as evidenced by the following case.

Case 7. A 30-year old female became "shaky" and developed gait difficulties. Seen two years later, she showed temporal pallor of the optic discs, nystagmus, scanning speech, ataxia, primarily on the right side, and a silly euphoria. The patient was again seen seven years later. The symptoms had increased. The most striking change was that she was not only silly and euphoric but intellectually deteriorated. She was fully oriented but at times illogical and irrational. There were no systematized delusions present but the patient showed complete lack of insight and judgment.

It is this type of case that is often seen in hospitals for chronic neurological conditions. Autopsy reports on such cases show severe destruction in the brain by plaques of multiple sclerosis.

The case histories of reactive depressions raise the question whether it is wise to apprise the patient of his diagnosis (Gallinek). No definite rules can be established and the decision has to be made on the basis of a thorough knowledge of the personality and environment of the patient. Tarlau,

after a poll of patients on this question, has concluded that, as a general rule, the physician should inform the patient. Our experiences do not confirm this view. We are inclined to agree with Binger who arrives at the conclusion that doctors should retain the right to decide what information would be useful to the individual patient. It is the doctor's task to help the patient to preserve as much of his functioning as possible. In a vast number of patients this could be best achieved by not acquainting them with the diagnosis that may have been made at a very early stage of the disease and that may possibly be followed by a long period of remission. If the diagnosis cannot be hidden from the patient, a great deal depends on the manner in which it is revealed to him. In discussing a disease with as capricious a course as multiple sclerosis, it is reasonable to stress the possibility of a mild form and of long remissions.

The management of reactive depression due to multiple sclerosis, as well as neurotic over-awareness of or overemphasis on physical symptoms, has to be conducted along general psychotherapeutic principles. Psychotherapy should primarily be of a supportive nature, but occasionally deeper analysis of neurotic attitudes may be necessary. Pharmacotherapy may be of limited help. We have recently started to use the various phenothiazine derivatives, chiefly chlorperazine, in order to mitigate the depressive repercussions of the physical incapacitation. We have achieved beneficial results in four patients whose concern and depression definitely decreased after the introduction of chlorperazine into their treatment program. This also may have led to a lessening of spasticity.

In those patients in whom the depressive reaction assumes severe and suicidal proportions, electroconvulsive therapy is indicated and can be given without any untoward effect on the organic pathology. The same applies to cases of major psychoses of affective or schizophrenic nature. This was true even prior to the introduction of succinylcholine. Naturally, since it has now become possible to administer electroconvulsive therapy without any marked motor manifestations, one will hesitate even less to treat a seriously depressed patient with multiple sclerosis in this way. It has to be kept in mind that only very serious reactive depressions will require this form of treatment and that all others will be best served with a psychotherapeutic approach.

Electroshock unmodified by succinylcholine never has been seen to cause flare-ups of the organic symptomatology which may indicate that physical stress is unlikely to precipitate attacks. On the other hand, we have formed the impression that emotional stress, as constituted by the depressive reactions to the physical incapacitation, in turn may not only cause superimposed additional pseudosomatic symptomatology but may also result in exacerbation of the organic disease process. It is also known that any neurological impairment when aggravated by an emotional disorder improves remarkably together with the removal of the psychiatric condition. Our observation on psychiatric symptoms in patients with multiple sclerosis emphasize that in such cases effective treatment of the psychiatric complications is an imperative need.

Summary and Conclusions

A cursory survey of the literature on mental changes in multiple sclerosis reveals agreement among authors only that mental changes are frequent. There is profound disagreement as to their nature and cause. Euphoria, eutonia, depression, intellectual and character changes as well as schizophrenic-like pictures have been described.

On the basis of their own experience, the authors cannot confirm the opinion that euphoria polysclerotica is the most frequently encountered mental change. The most frequent psychiatric manifestation in multiple sclerosis is the reactive depression which occurs as a reaction to the actual or anticipated disability. It may be associated with neurotic over-awareness of factually minor symptoms. Impairment of motor power, forced retirement, sphincteric disturbances are most likely to cause reactive depressions. The predominance of depressive reactions in the authors' material is probably explained by the fact that their cases were private patients, seen in fairly early stages of the disease. Other authors who stressed euphoria had chiefly studied hospitalized, advanced cases.

What has been described as euphoria appears to be more a bland state of indifference and absence of concern about the disability than true euphoria. These changes resemble somewhat the indifference achieved by lobotomy or by the various phenothiazine derivatives. It may be assumed that the state of emotional indifference is due to anatomic lesions. It has been seen in the early as well as in the late stages of the disease. Independent major psychoses may occur in multiple sclerosis patients perhaps more frequently than in other individuals. They may be endogenous depressions or true schizophrenia not at all related to the neurological disease. These major psychoses should not be confused with short-lasting psychotic episodes during acute flare-ups of the neurological disorder which are of "symptomatic organic nature." In advanced cases, there is progressive mental deterioration, occasionally associated with silly euphoria, due to anatomic changes caused by the neurological disease.

The reactive depressions require psychotherapy and the emotional repercussions of the physical incapacitation can be mitigated by pharmacotherapy. Chlorperazine has proven to be useful. In severe and suicidal reactive depressions and in independent major psychoses of affective or schizophrenic nature, electric shock therapy has been given without any harmful effect on the organic disease. Since it appears possible, although not proven, that emotional stress may result in exacerbation of the organic disease process, all psychiatric complications in multiple sclerosis should receive effective psychiatric therapy.

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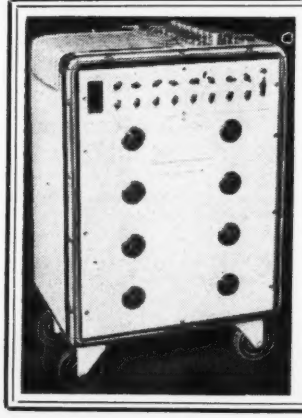

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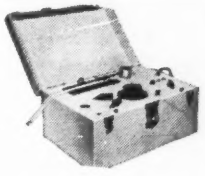

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